PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 February 2001 (05.02.01)	
International application No. PCT/SE00/01267	**Applicant's or agent's file reference** 2001547
International filing date (day/month/year) 15 June 2000 (15.06.00)	**Priority date** (day/month/year) 15 June 1999 (15.06.99)
Applicant SKOGVALL, Staffan	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 December 2000 (06.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT
REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired)(12 characters maximum)* 2001547

Box No. I TITLE OF INVENTION

RECEPTOR AGONISTS AND ANTAGONISTS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Respiratorius AB
Sölvegatan 41
SE-223 70 LUND
SWEDEN

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: SWEDEN

State *(that is, country)* of residence: SWEDEN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR /FURTHER INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Staffan Skogvall
Flygelvägen 33
SE-224 72 LUND
SWEDEN

This person is:

☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SWEDEN

State *(that is, country)* of residence: SWEDEN

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

AWAPATENT AB
Box 5117
SE-200 71 MALMÖ
SWEDEN

Telephone No.
+46 40 98 51 00

Facsimile No.
+46 40 26 05 16

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldovia, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)*

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒	AE	United Arab Emirates	
☒	AL	Albania	
☒	AM	Armenia	
☒	AT	Austria	+Utility Model
☒	AU	Australia	
☒	AZ	Azerbaijan	
☒	BA	Bosnia and Herzegovina	
☒	BB	Barbados	
☒	BG	Bulgaria	
☒	BR	Brazil	
☒	BY	Belarus	
☒	CA	Canada	
☒	CH and LI	Switzerland and Liechtenstein	
☒	CN	China	
☒	CR	Costa Rica	
☒	CU	Cuba	
☒	CZ	Czech Republic	+Utility Model
☒	DE	Germany	+Utility Model
☒	DK	Denmark	+Utility Model
☒	DM	Dominica	
☒	EE	Estonia	+Utility Model
☒	ES	Spain	
☒	FI	Finland	+Utility Model
☒	GB	United Kingdom	
☒	GD	Grenada	
☒	GE	Georgia	
☒	GH	Ghana	
☒	GM	Gambia	
☒	HR	Croatia	
☒	HU	Hungary	
☒	ID	Indonesia	
☒	IL	Israel	
☒	IN	India	
☒	IS	Iceland	
☒	JP	Japan	
☒	KE	Kenya	
☒	KG	Kyrgyzstan	
☒	KP	Democratic People's Republic of Korea	
☒	KR	Republic of Korea	+Utility Model
☒	KZ	Kazakhstan	
☒	LC	Saint Lucia	
☒	LK	Sri Lanka	
☒	LR	Liberia	
☒	LS	Lesotho	
☒	LT	Lithuania	
☒	LU	Luxembourg	
☒	LV	Latvia	
☒	MA	Morocco	
☒	MD	Republic of Moldova	
☒	MG	Madagascar	
☒	MK	The former Yugoslav Republic of Macedonia	
☒	MN	Mongolia	
☒	MW	Malawi	
☒	MX	Mexico	
☒	NO	Norway	
☒	NZ	New Zealand	
☒	PL	Poland	
☒	PT	Portugal	
☒	RO	Romania	
☒	RU	Russian Federation	
☒	SD	Sudan	
☒	SE	Sweden	
☒	SG	Singapore	
☒	SI	Slovenia	
☒	SK	Slovakia	+Utility Model
☒	SL	Sierra Leone	
☒	TJ	Tajikistan	
☒	TM	Turkmenistan	
☒	TR	Turkey	
☒	TT	Trinidad and Tobago	
☒	TZ	United Republic of Tanzania	
☒	UA	Ukraine	
☒	UG	Uganda	
☒	US	United States of America	
☒	UZ	Uzbekistan	
☒	VN	Viet Nam	
☒	YU	Yugoslavia	
☒	ZA	South Africa	
☒	ZW	Zimbabve	

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DZ Algeria ☒ MZ Mozambique

☒ AG Antigua and Barbuda

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☒ Further priority claims are indicated in the Supplement Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 15 June 1999 (15.06.99)	9902251-9	SWEDEN		
item (2) 15 June 1999 (15.06.99)	9902252-7	SWEDEN		
item (3) 28 April 2000 (28.04.00)	SE00/00819			SWEDEN

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1-3

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

See continuation sheet No.3b enclosed

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	: 5
description (excluding sequence listing part)	: 31
claims	: 9
abstract	: 1
drawings	: 1
sequence listing part of description	:
Total number of sheets	: 47

Figure of the drawings which should accompany the abstract: 1

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference No., if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international applications into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): Subauthorisation. Copies of ITS-Reports

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

15 June 2000

Dan Henriksson

Authorised Agent

For receiving Office use only

1.	Date of actual receipt of the Purported international application:	2. Drawings: ☐ received: ☐ not received:
3.	Corrected date of actual receipt due to later but Timely received papers or drawings completing the purported international application:	
4.	Date of timely receipt of the required Corrections under PCT Article 11(2):	
5.	International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Supplement Box of Box No. VI	**PRIORITY CLAIM**	
Filing date of earlier application (day/month/year)	Number of earlier application	National application: country
Item (4) **17 June 1999** **(17.06.99)**	**60/139 632**	**USA**
Item (5) **17 June 1999** **(17.06.99)**	**60/139 633**	**USA**

Continuation of Box No. VII INTERNATIONAL SEARCHING AUTHORITY		
Request to use results of earlier search; reference to that search:		
Date (day/month/year)	Number	Country (or regional Office)
15.06.1999 15.06.1999	SE99/00813 SE99/00814	SWEDEN SWEDEN

11/1-01 Vidi! Inget åtgärd. /DB

WO 00/76500
PCT/SE00/01267

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:
AWAPATENT AB
Box 5117
S-200 71 Malmö
SUÈDE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 21 December 2000 (21.12.00)	
Applicant's or agent's file reference 2001547	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/SE00/01267	15 June 2000 (15.06.00)	15 June 1999 (15.06.99)

Applicant
RESPIRATORIUS AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   21 December 2000 (21.12.00) under No. WO 00/76500

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

ENT COOPERATION TREAT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Awapatent AB
Box 5117
200 71 MALMÖ

RECEIVED
2000 -12- 07
AWAPATENT, Malmö

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)* 06-12-2000

Applicant's or agent's file reference
2001547 /DH

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01267	15-06-2000	15-06-1999

Applicant
RESPIRATORIUS AB
et al

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:
   06-12-2000

2. This date of receipt is:

   [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

   [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

   [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

   [ ] *(If applicable)* This notificaton confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/
Patent- och registreringsverket
Box 5055
S-102 42 STOCKHOLM
Facsimile No. 08-667 72 88
Telex
17978
PATOREG-S

Authorized officer
Hilkka Kamppinen
Telephone No. 08-782 25 00

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76500 A3

(51) International Patent Classification[7]: A61K 31/395, A61P 11/08

(21) International Application Number: PCT/SE00/01267

(22) International Filing Date: 15 June 2000 (15.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9902251-9	15 June 1999 (15.06.1999)	SE
9902252-7	15 June 1999 (15.06.1999)	SE
60/139,633	17 June 1999 (17.06.1999)	US
60/139,632	17 June 1999 (17.06.1999)	US
PCT/SE00/00819	28 April 2000 (28.04.2000)	SE

(71) Applicant *(for all designated States except US)*: **RESPIRATORIUS AB** [SE/SE]; Sölvegatan 41, S-223 70 Lund (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SKOGVALL, Staffan** [SE/SE]; Flygelvägen 33, S-224 72 Lund (SE).

(74) Agent: **AWAPATENT AB**; Box 5117, S-200 71 Malmö (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
12 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/76500 A3

(54) Title: COMPOUND FOR USE AS A MEDICAMENT FOR TREATMENT OF DISORDERS INVOLVING BRONCHOCONTRACTION

(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use f said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronochial asthma attack"; & 63015, SU,A1,1701320, 19911230 --	5
A	US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95) --	5
A	WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97) --	5

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2001	03 -04- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Lille Médical, Volume 16, No 5, 1971, F. Guerrin et al, "Effets du métoclopramide sur le bronchospasme expérimental du cobaye et sur le test à l'acétylcholine chez l'homme" page 731 - page 735	12
X	Arch.int.Pharmacodyn, Volume 165, No 2, 1967, J. Simke et al, "Bradykinin induced bronchoconstriction in guinea pigs and its modification by various agents" page 291 - page 301	12
X	British Journal of Anaesthesia, Volume 78, 1997, N. Otomo et al, "In vivo assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope" page 579 - page 582	12
X	Clinical and Experimental Pharmacology and Physiology, Volume 19, 1992, M.P. Rechtman, "Sensory nerves in the airways as a target for drug development" page 31 - page 39	12
X	Br.J.Pharmacol., Volume 101, 1990, M.P. Rechtman et al, "Effects of morphine, H-Tyr-D-Arg-Phe-Lys-NH2(DALDA) and B-HT920 on non-cholinergic nerve-mediated bronchoconstriction in pithed guinea-pigs" page 269 - page 272	12
X	ANESTH ANALG, Volume 72, 1991, Benoît Gentil et al, "Droperidol Prevents Serotonin-Induced Bronchospasm in the Guinea Pig" page 612 - page 615	12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Japan.J.Pharmacol., Volume 51, 1989, Shahin Sanjar et al, "The Effect of Prophylactic Anti-Asthma Drugs on PAF-Induced Airway Hyperreactivity" page 151 - page 160	12
X	J.Pharmacobio-Dyn., Volume 12, 1989, Yoshio Tsuchiya et al, "Inhibition of the Vagal Reflex-Induced Tracheal Constriction by Psychotropic Drugs" page 437 - page 440	12
X	EUROPEAN JOURNAL OF PHARMACOLOGY, Volume 6, 1969, Enrique Hong et al, "Similarities between the Pharmacological Actions of Quipazine and Serotonin" page 274 - page 280	12
X	WO 8904660 A1 (BEECHAM GROUP PLC), 1 June 1989 (01.06.89)	12
X	Proceedings of the Society for Experimental Biology and Medicine, Volume 184, 1987, L.B. Lipham et al, "Quipazine-Metoclopramide Inhibition of CB-154-Induced Prolactin Suppression in Rats: Neurotransmitter-Metabolite Correlations (42475)" page 250 - page 255	17
X	Indian J Med Res, Volume 78, October 1983, T.J. Hemnani & P.G. Dashputra, "Potentiation of the psychotropic effect of chlorpromazine by metoclopramide" page 593 - page 595	17
X	Anti-Cancer Drugs, Volume 7, 1996, Vittorio Gebbia et al, "Treatment of cisplatin-related nausea and vomiting with a combination of ondansetron and metoclopramide: a pilot study" page 734 - page 737	17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Br.J Clin Pharmacol, Volume 41, 1996, D.T.T. Chua et al, "The antiemetic efficacy of tropisetron plus dexamethasone as compared with conventional metoclopramide-dexamethasone combination in Orientals receiving cisplatin chemotherapy: a randomized crossover trial" page 403 - page 408	17
	--	
X	Journal of Clinical Anesthesia, Volume 10, 1998, Richard A. Steinbrook et al, "Prophylactic Antiemetics for Laparoscopic Cholecystectomy: A Comparison of Perphenazine, Droperidol Plus Ondansetron, and Droperidol Plus Metoclopramide" page 494 - page 498	17
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01267

Box I **Observations where certain claims were found unsearchable (Continuati n f item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7 and 16
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☒ Claims Nos.: 1-6,8-15 and 17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet*

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

S e extra sheet**

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

*The claims contain a plurality of different compounds and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT to such an extent that a meaningful search of the whole scope of the claims is impossible.

Expressions such as "compound ... having agonist activity to a 5-HT4 receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Further, expressions such as "disorders involving bronchocontraction" and "derivatives" are not clear and concise.

Due to these deficiencies, a search has been carried out for those parts of the claims which appear to be supported and disclosed, namely claim 5 (invention 1), the part of claim 12 which refers to claim 11 (invention 2) and the combination of the compounds according to claims 5 and 12 (invention 3).

The search has been aimed at documents having explicit information of use for treatment of bronchocontraction.

The applicants attention is drawn to the fact that claims relating to those parts of the inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01267

**As is stated in Annex B to Administrative Instructions under the PCT, in force July 1, 1998, (PCT GAZETTE 1998, June 25, pp 45-50) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features"- i.e. features that define a contribution which each of the inventions makes over the prior art (cf. PCT Rule 13.2). This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

Invention 1. Claims 1-7 relating to a compound having agonist activity to a 5-HT4 receptor.

Invention 2. Claims 8-12 relating to a compound having antagonist activity to a 5-HT3 receptor.

Invention 3. Claims 13-17 relating to a composition comprising a combination of compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/01267

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5418241 A	23/05/95	AU 659033 B	04/05/95
		AU 4860593 A	14/04/94
		CA 2107060 A	29/03/94
		CN 1087340 A	01/06/94
		CZ 9302014 A	13/04/94
		EP 0591026 A	06/04/94
		FI 934220 A	29/03/94
		FR 2696176 A,B	01/04/94
		HU 65396 A	28/06/94
		HU 211490 B	28/11/95
		HU 9302726 D	00/00/00
		HU 9500434 A	28/09/95
		IL 107132 D	00/00/00
		JP 6192254 A	12/07/94
		MX 9305930 A	30/06/94
		NO 933434 A	29/03/94
		NZ 248775 A	24/02/95
		PL 172852 B	31/12/97
		PL 300514 A	05/04/94
		SK 103293 A	10/08/94
		ZA 9307155 A	23/05/94
WO 9717345 A1	15/05/97	AT 181328 T	15/07/99
		AU 707325 B	08/07/99
		AU 7500196 A	29/05/97
		BG 102412 A	31/08/99
		BR 9611311 A	29/06/99
		CA 2236357 A	15/05/97
		CN 1202169 A	16/12/98
		CZ 9801421 A	12/08/98
		DE 69602970 D,T	20/01/00
		EP 0863897 A,B	16/09/98
		SE 0863897 T3	
		ES 2135934 T	01/11/99
		FR 2741069 A,B	16/05/97
		GR 3030823 T	30/11/99
		IL 124364 D	00/00/00
		JP 2000500125 T	11/01/00
		NO 982092 A	29/06/98
		NZ 321626 A	28/10/98
		PL 326671 A	12/10/98
		SI 863897 T	00/00/00
		SK 59998 A	04/11/98
		TR 9800827 T	00/00/00
		US 5929089 A	27/07/99
		FR 2741070 A,B	16/05/97
		FR 2745574 A,B	05/09/97

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/01267

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8904660 A1	01/06/89	AT 78162 T	15/08/92
		AU 616706 B	07/11/91
		AU 2626488 A	14/06/89
		DE 3872872 A,T	20/08/92
		DK 345889 A	12/07/89
		EP 0340270 A,B	08/11/89
		SE 0340270 T3	
		GB 8726716 D	00/00/00
		JP 2502185 T	19/07/90
		US 5098909 A	24/03/92
		GB 8726717 D	00/00/00

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC-2001547	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE00/01267	International filing date *(day/month/year)* 15.06.2000	Priority date *(day/month/year)* 15.06.1999
International Patent Classification (IPC) or national classification and IPC7 A61K 31/395, A61P 11/08		
Applicant RESPIRATORIUS AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 34 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.12.2000	25.10.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08 667 72 88	Telex 17978 PATOREG-S
	Authorized officer Eva Johansson/BS

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP00/01267

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-32 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under article 19
pages _____ , filed with the demand
pages 33-36, 38-53, 55-66 , filed with the letter of 2001-09-19

☐ the drawings: 37, 54 2001-10-23
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01267

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 4,8,12-13

because:

☒ the said international application, or the said claims Nos. 4,8,12-13
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,5,9-10
are so unclear that no meaningful opinion could be formed *(specify)*:

The claims contain such a plurality of different compounds and parameters so that it was impossible to search the whole scope of the claims. As the search was carried out for those parts of the claims, which appear to be supported and disclosed, the written opinion and examination report will be based on the same principle as the search

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01267

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

As is stated in Annex B to Administrative Instructions under the PCT, in force July 1, 1998, (PCT GAZETTE1998, June 25, pp 45-50) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features" - i.e. features that define a contribution which each of the inventions makes over the prior art (cf. PCT Rule 13.2). This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

Invention 1: Claims 1-4 relating to a compound having agonist activity to a 5-HT4 receptor.

Invention 2: Claims 5-8 relating to a compound having antagonist activity to a 5-HT3 receptor.

Invention 3: Claims 9-13 relating to a composition comprising a combination of compounds from invention 1 and invention 2.

INTERNATIONAL PRELIM[illegible]RY EXAMINATION REPORT

International application No.
PCT/SE00/01267

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3,5-7,9-10	YES
	Claims		NO
Inventive step (IS)	Claims	1-3,5-7,9-10	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-3,5-7,9-10	YES
	Claims	4,8,12-13	NO

2. Citations and explanations (Rule 70.7)

The claimed invention relates to the use of compounds having agonist activity to a 5-HT_4 receptor, to the use of compounds having antagonist activity to a 5-HT_3 receptor and to the use of a composition comprising a combination of the two groups of compounds in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction.

New claims have been filed 19 September 2001. The claims have been restricted to second medical use claims.

The expression " depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia" has been deleted and instead the expression "asthma and disorders related thereto, emphysema, chronic bronchitis and chronic obstructive pulmonary disease" has been inserted in the new claims 1, 5 and 9. The new expression has support in the description.

The claims still contain a plurality of different compounds (the search is not complete as is stated in the search report). The examination report will be based on the documents cited in the search report and can therefore not be considered to be complete.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

The following documents are cited in the search report:

D1 STN International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronochial asthma attack"; & 63015, SU,A1,1701320, 19911230

D2 US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95)

D3 WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97)

D4 Lille Médical, Volume 16, No 5, 1971, F. Guerrin et al, "Effets du métoclopramide sur le bronchospasme expérimental du cobaye et sur le test á l'acétylcholine chez l'homme" page 731 - page 735

D5 Arch.int.Pharmacodyn, Volume 165, No 2, 1967, J. Simke et al, Bradykinin induced bronchoconstriction in guinea pigs and its modification by various agents" page 291 - page 301

D6 British Journal of Anaesthesia, Volume 78, 1997, N. Otomo et al, "In vivo assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope" page 579 - page 582

D7 Clinical and Experimental Pharmacology and Physiology, Volume 19, 1992, M.P. Rechtman, "Sensory nerves in the airways as a target for drug development" page 31 - page 39

D8 Br. J. Pharmacol., Volume 101, 1990, M.P. Rechtman et al, "Effects of morphine, H-Tyr-D-Arg-Phe-Lys-NH2(DALDA) and B-HT920 on non-cholinergic nerve-mediated bronchoconstriction in pithed guinea-pigs" page 269 - pge 272

D9 ANESTH ANALG, Volume 72, 1991, Benoit Gentil et al, "Droperidol Prevents Serotonin-Induced Bronchospasm in the Guinea Pig" page 612 - page 615

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

D10 Japan.J.Pharmacol., Volume 51, 1989, Shahin Sanjar et al, "The Effect of Prophylactic Anti-Asthma Drugs on PAF-Induced Airway Hyperreactivity" page 151 - page 160

D11 J.Pharmacobio-Dyn., Volume 12, 1989, Yoshio Tsuchiya et al, "Inhibition of the Vagal Reflex-Induced Tracheal Constiction by Psychotropic Drugs" page 437 - page 440

D12 EUROPEAN JOURNAL OF PHARMACOLOGY, Volume 6, 1969, Enrique Hong et al, "Similarities between the Pharmacological Actions of Quipazine and Serotonin" page 274 - page 280

D13 WO 8904660 A1 (BEECHAM GROUP PLC), 1 June 1989 (01.06.89)

D14 Proceedings of the Society for Experimental Biology and Medicine, Volume 184, 1987, L.B. Lipham et al, "Quipazine-Metoclopramide Inhibition of CB-154-Induced Prolactin Suppression in Rats: Neurotransmitter-Metabolite Correlations (42475)" page 250 - page 255

D15 Indian J Med Res, Volume 78, October 1983, T.J. Hemnani & P.G. Dashputra, "Potentiation of the psychotropic effect of chlorpromazine by metoclopramide" page 593 - page 595

D16 Anti-Cancer Drugs, Volume 7,.1996, Vittorio Gebbia et al, "Treatment of cisplatin-related nausea and vomiting with a combination of ondansetron and metoclopramide: a pilot study" page 734 - page 737

D17 Br.J Clin Pharmacol, Volume 41, 1996, D.T.T. Chua et al, "The antiemetic efficacy of tropisetron plus dexamethasone as compared with conventional metoclopramide-dexamethasone chemotherapy: a randomized crossover trial" page 403 - page 408

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

D18 Journal of Clinical Anesthesia, Volume 10, 1998
Richard A. Steinbrook et al, "Prophylactic Antiemetics for Laparoscopic Cholecystectomy: A Comparison of Perphenazine, Droperidol Plus Ondansetron, and Droperidol Plus Metoclopramide"
page 494 - page 498

D1) describes a method for stopping bronchial asthma attacks by inhaling a serotonin solution.

D2) and D3) relate to compounds which can be used for treating and preventing disorders in which 5-HT_4 receptors are involved, in D2) for example respiratory disorders.

These compounds are not included in the scope of the new claim 1. Thus, the cited documents relate to the general state of art and are not considered to be of particular relevance.

Claims 1-3 are considered to be new and have inventive step.

In D4) the effects of metoclopramide on experimental bronchospasms are described.

D5) describes the inhibitory effect of several compounds, for example chlorpromazine, on bradykinin induced bronchocontraction

D6) relates to droperidol-induced bronchial relaxation, which is thought to be, at least in part, due to 5-HT receptor antagonism and D9) shows the use of droperidol to prevent serotonin-induced bronchospasm.

In D11) chlorpromazine and imipramine are shown to reduce reflex tracheal contraction which is involved in for example asthma.

D12) describes the effects of quipazine for example induction of bronchoconstriction in guinea pigs. This effect is antagonised by methysergide.

Metoclopramide, chlorpromazine, droperidol, imipramine, quipazine and methysergide are excluded from the new claim 5.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

D7) and D8) both describe different compounds that can inhibit non-cholinergic nerve-mediated bronchoconstriction for example B-HT920 which is talipexole dihydrochloride.

D10) relate to anti-asthma drugs.

D13) relates to the use of 5-HT_3 receptor antagonists for the treatment of cough and bronchoconstriction to inhibit airway contraction caused by inhalation of capsaicin and there is information if the substances are able to inhibit asthmatic bronchocontraction.

None of the cited documents discloses the use of 5-HT_3 receptor antagonists for the treatment of human asthma, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease. A person skilled in the art would not conclude, from reading the document, that 5-HT_3 receptor antagonists can be used for the treatment of humans.

Consequently, the cited documents only disclose the general state of the art, and are not considered to be of particular relevance.

Thus, claims 5-7 are considered to be new and have inventive step.

The combination of quipazine and metoclopramide for suppression of CB-154-induced prolactin is described in D14) while D15) relates to the potentiation of the psychotropic effect of chlorpromazine by metoclopramide.

In D16) the use of a combination of metoclopramide and ondansetron as antiemetic therapy is described.

D17) relates to a comparison between tropisetron-dexamethasone and metoclopramide-dexamethasone.

In D18) the efficiency of different drugs and drug combinations, for example droperidol plus metoclopramide, as prophylactic antiemetics for laparoscopic cholecystectomy is studied.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

D14)-D18) relate to a combination a 5-HT_4 receptor agonist and a 5-HT_3 receptor antagonist.
There is no information in the cited documents about the treatment of disorders involving human bronchocontraction.

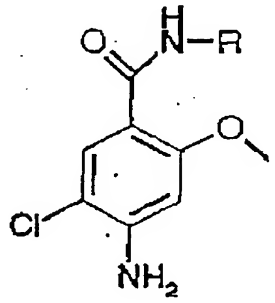
Consequently, the cited documents only disclose the general state of the art, and are not considered to be of particular relevance.

Thus, claims 9-11 are considered to be new and have inventive step.

Claims 4, 8 and 12-13 relate to methods for therapeutic treatment. Claims of this kind may be accepted and examined in some countries.
However, owing to the difference in national practice and law, it is not possible for the International Preliminary Authority to give a statement on such claims that would be equally valid for all states. The consideration given thereafter must therefore be based on the acceptance on such claims according to national legislation.

CLAIMS

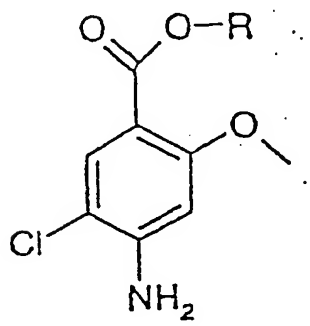
1. Use of one or more compounds having agonist activity to a 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising the following 5-HT_4 receptor agonists: benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopramide, with the structural formula:



having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

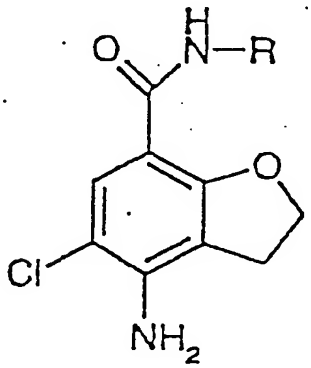
AMENDED SHEET

benzoic acid esters:

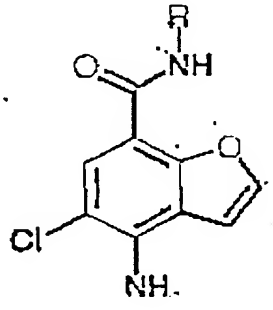


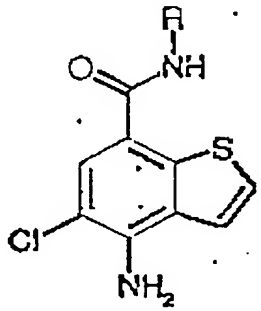
preferably ML 10302, RS 57639, and SR 59768;

a 2,3-dihydro-bensofuran-7-carboxamide compound, preferably ADR 932, Prucalopride (=R 093877), and SK-951;

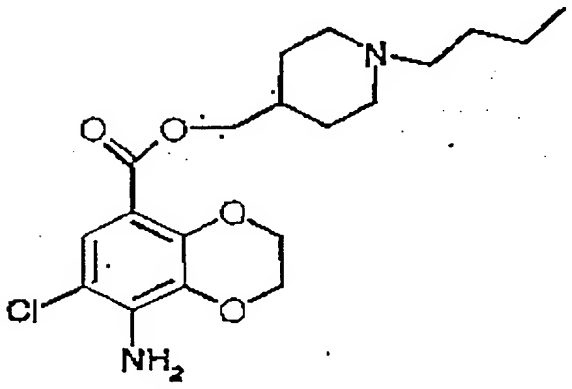


benzofuranes and benzotiophenes,



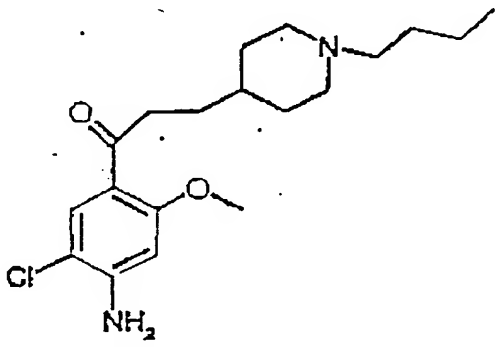


the benzodioxan

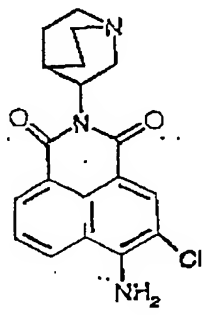


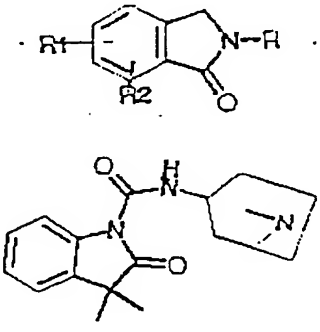
SB 204070

the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone



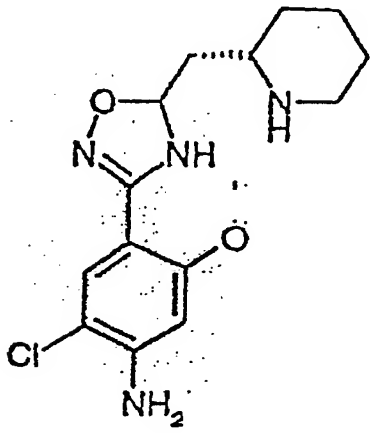
e.g. preferably RS 67333 and RS 17017;
naphtalimides, preferably RS 56532;





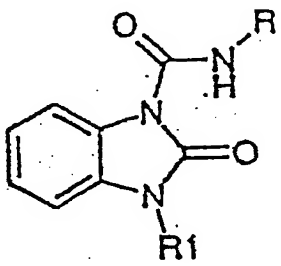
benzindolones;

compounds in which the amide function has been replaced with an oxadiazol ring;



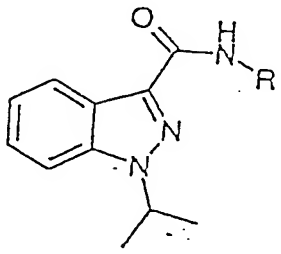
preferably YM-53389;

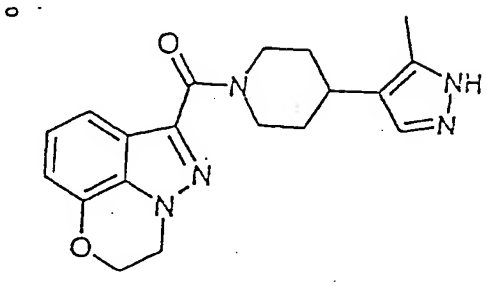
benzimidazolone-1-carboxamides



preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

the carboamides

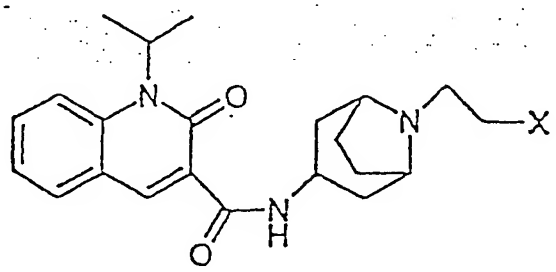




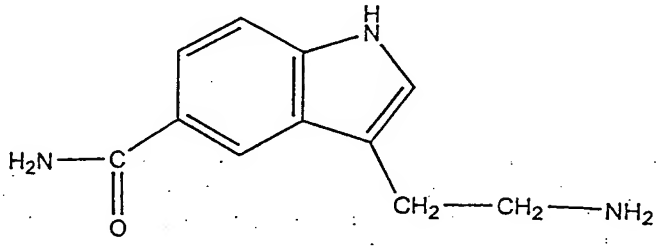
indols, preferably 5-methoxytryptamine, 2-methyl-serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side chain:

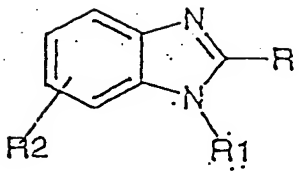
benzokinolinones



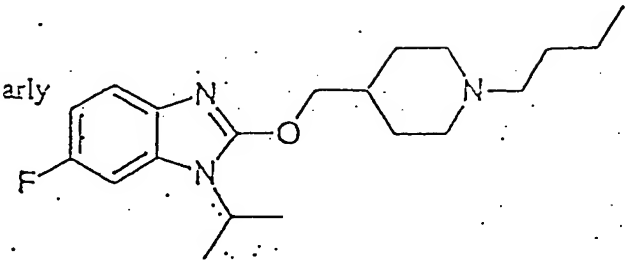
5-carboxamidotryptamine (5-CT), with the structural formula:



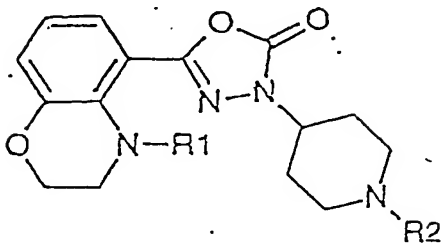
3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,



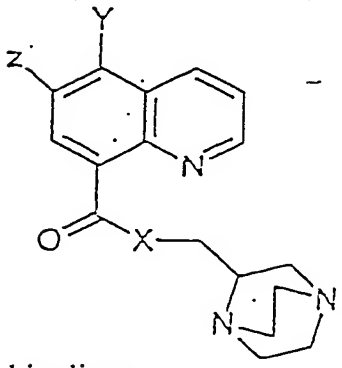
, particularly



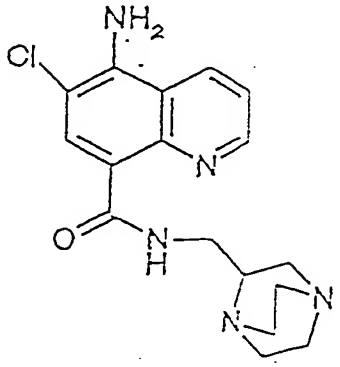
2-piperidinmethylethers
of bensimidazol



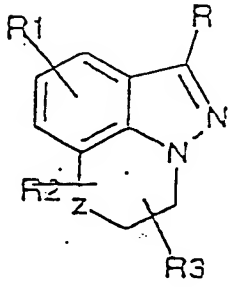
oxadiazalon based
substance



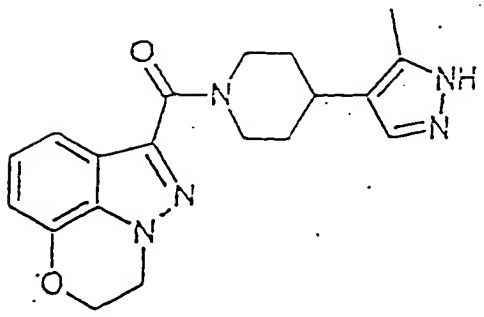
, particularly

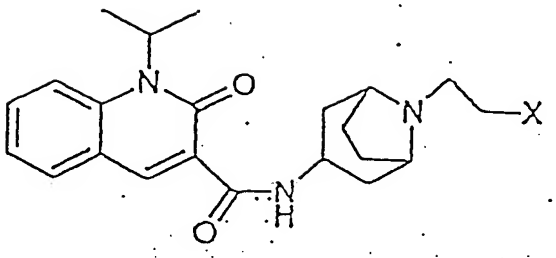


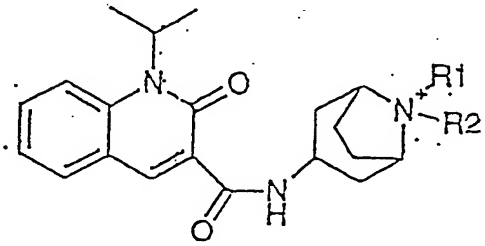
kinolines



, particularly







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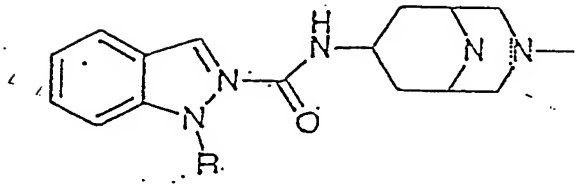

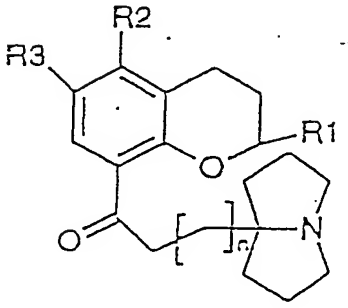

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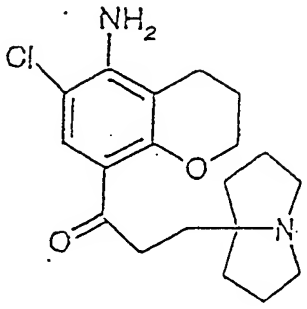
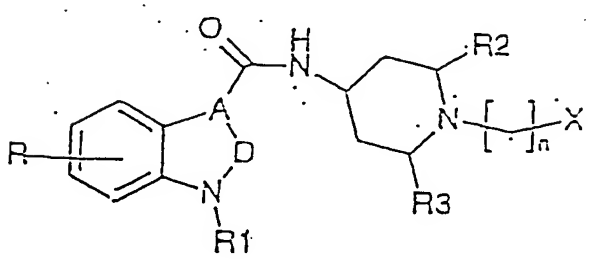
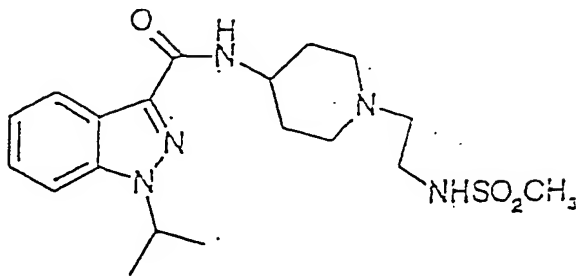


benzopyranes





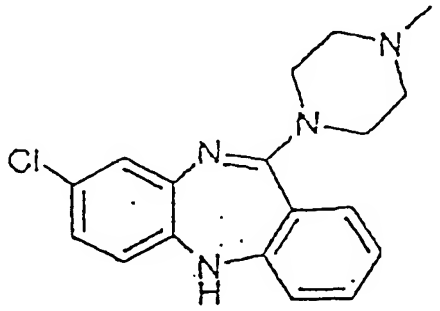
and derivatives and pharmaceutically acceptable salts thereof.

2. Use according to claim 1, wherein said compound is VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine, Zacopride, RS56532, Mosapride, BRL 24924, or SC 53116.

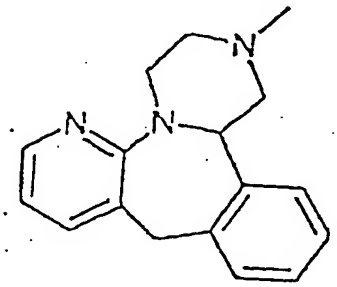
3. Use according to any one of the previous claims, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

4. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according to any one of claims 1 and 2.

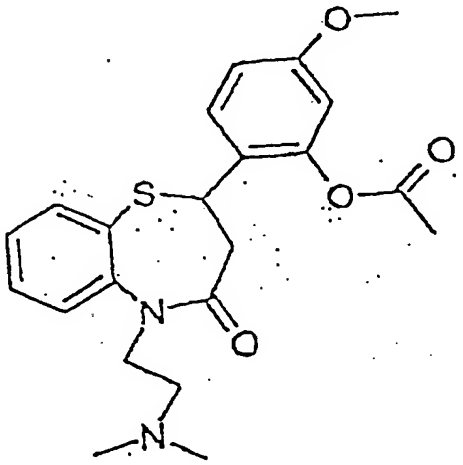
5. Use of one or more compounds having antagonist activity to a 5-HT_3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 5-HT_3 receptor antagonists



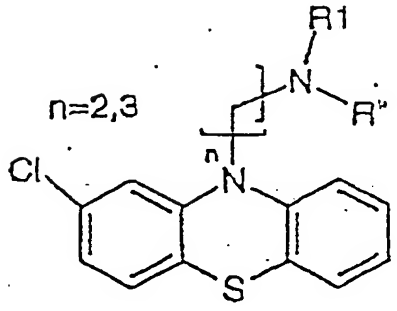
benzazepines, preferably mirtazapine



benztiazephines, preferably diltiazem

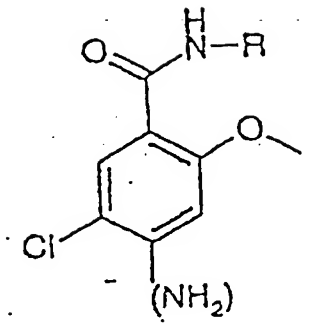


and fentiazines



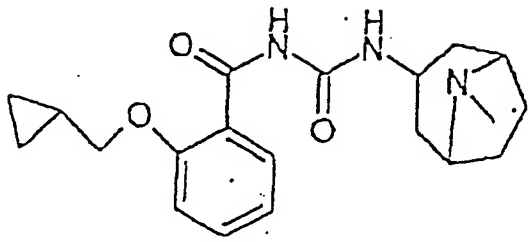
preferably perphenazine, stemetil;

compounds also having 5-HT_4 receptor agonist activity, preferably benzamides



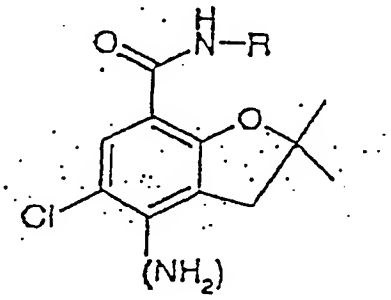
(cisapride, zacopride, mosapride, pancropride, BRL 24924, BMY 33462)

and



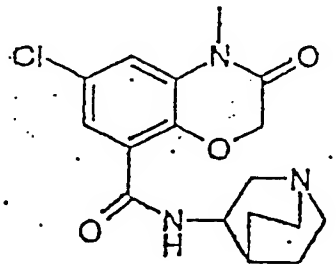
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



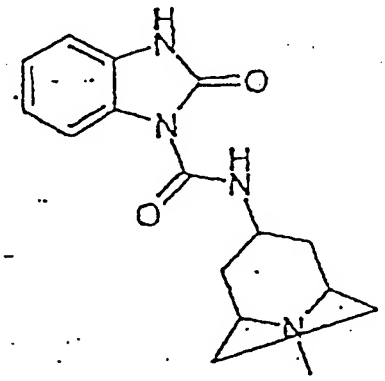
(preferably zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides



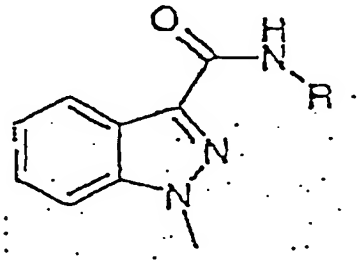
preferably azasetron (=Y25130);

benzimidazolones



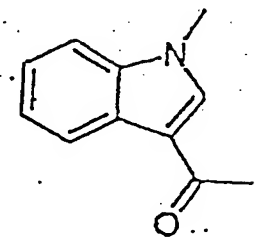
preferably itasetron (=DAU 6215);

indazol-3-carboxamides

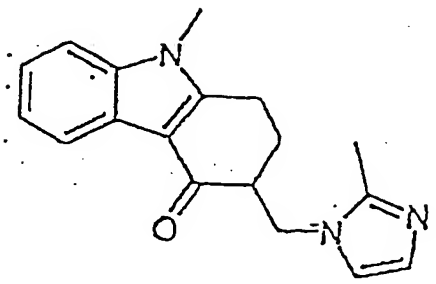


preferably N 3389, LY 278584, DAT 582;

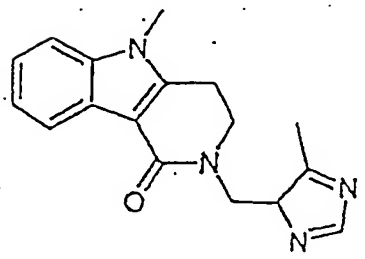
wherein the latter group reminds most of the specific 5-HT_3 antagonists, which contains the group



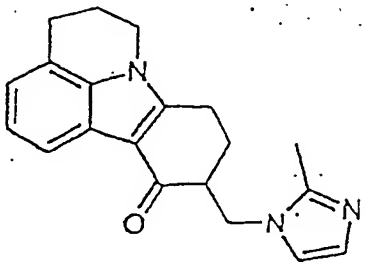
in different forms, such as



ondansetron

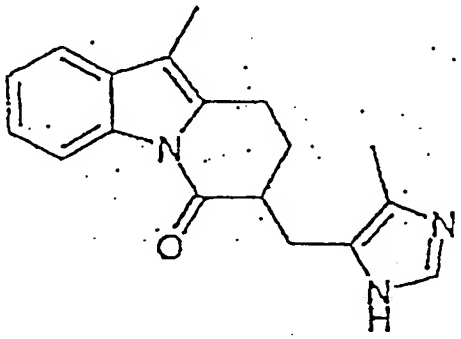


alosetron



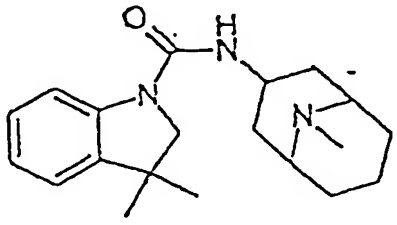
cilansetron

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen



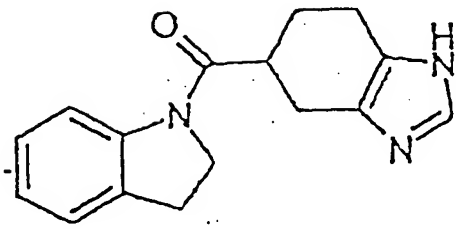
FK 1052

also being an antagonist against both 5-HT_3 and 5-HT_4 receptors,



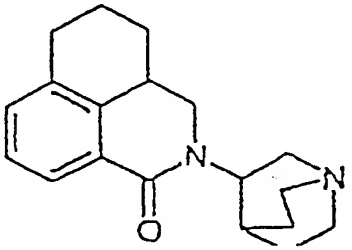
BRL 46470 A

bisindoles

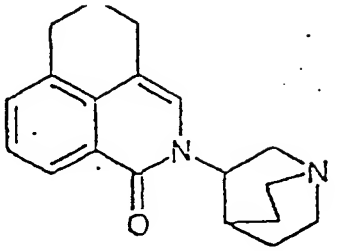


YM 114

isoquinoline-1-ones

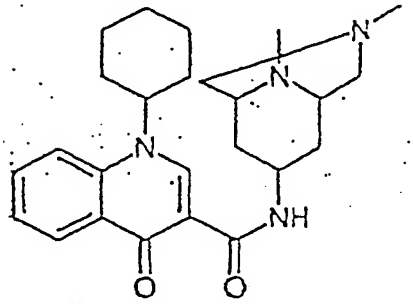


palonosetron (=RS 25259-197)

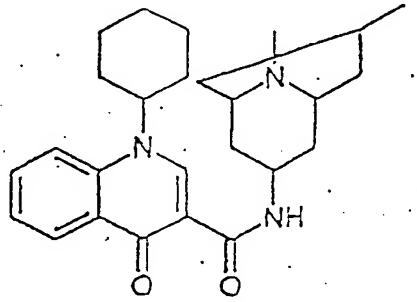


RS 42358-197

and the quinoline-3-carboxamides

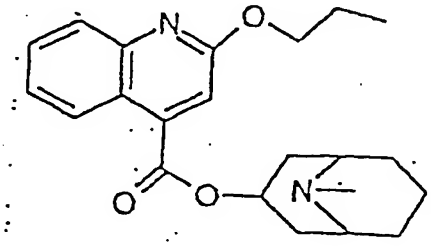


WAY-SEC 579

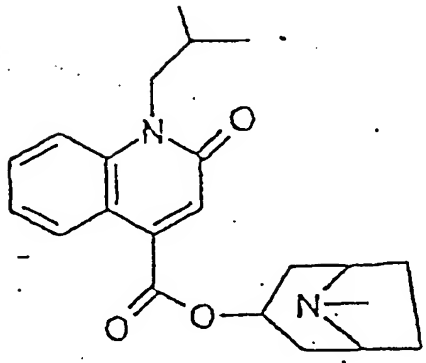


Mirisetron (=WAY 100579),

quinoline-4-carboxylates

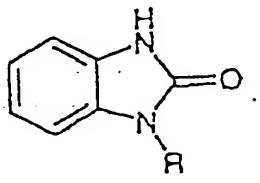


preferably KF 17643



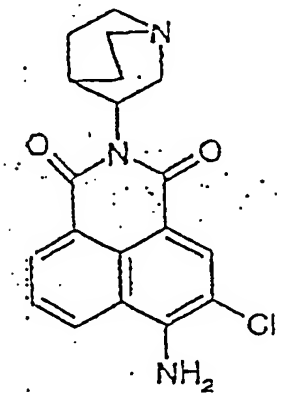
preferably KF 18259;

benzimidazolones



preferably itasetron (DAU6215),

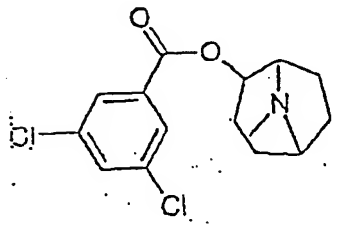
and the naphtimides



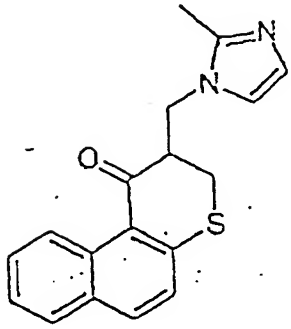
RS 56532

preferably RS 56532;

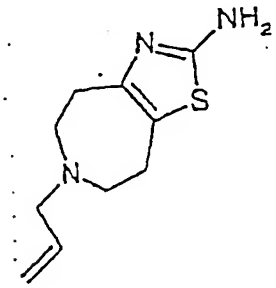
MDL 72222, which also is a specific 5-HT_3 antagonist;



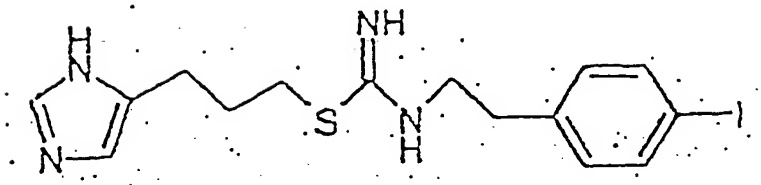
; and



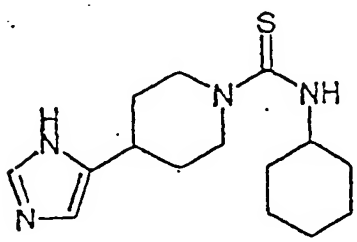
GK 128



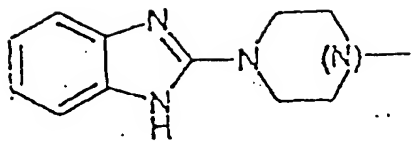
Talipexole



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide, Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect,

and derivatives and pharmaceutically acceptable salts thereof.

6. Use according to claim 5, wherein said compound is Tropanyl 3,5-dimethylbenzoate, MDL 72222, SDZ 216-525, ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron, or Cilansetron.

7. Use according to any one of claims 5 and 6, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

8. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according to any one of claims 5 and 6.

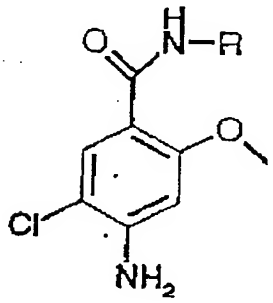
9. Use of a composition comprising a combination of at least one compound with agonist activity to the 5-HT_4 receptor, and at least one compound with antagonist activity to the 5-HT_3 receptor, for the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, preferably asthma and disorders related thereto.

10. Use according to claim 9, wherein said composition has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said combination is chosen from the following groups of

a) 5-HT_4 receptor agonists:

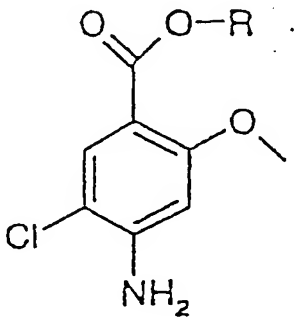
benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopra

mide, with the structural formula:



having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

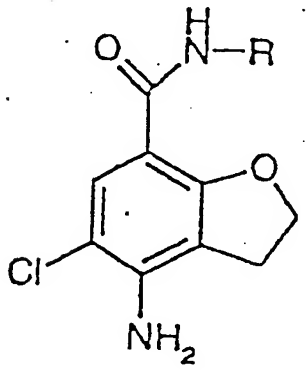
benzoic acid esters:



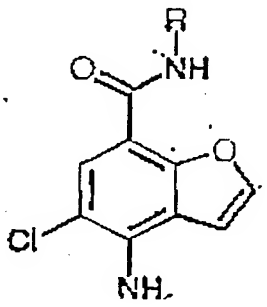
preferably ML 10302, RS 57639, and SR 59768;

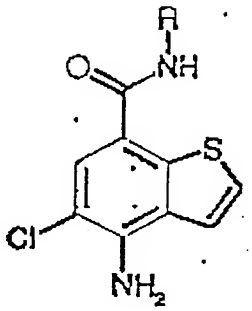
a 2,3-dihydro-bensofuran-7-carboxamide compound,

preferably ADR 932, Prucalopride (=R 093877), and SK-951;

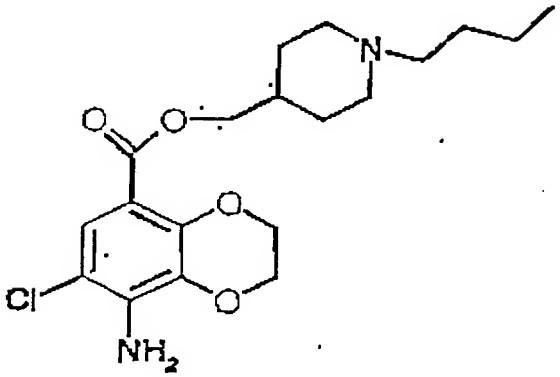


benzofuranes and benzotiophenes,



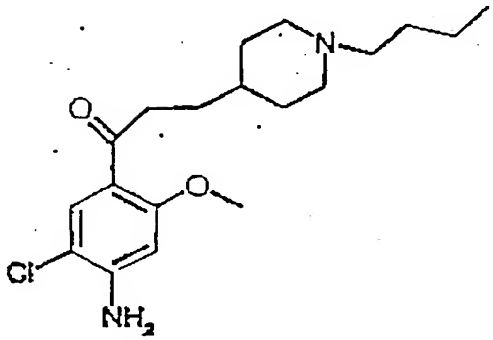


the benzodioxan



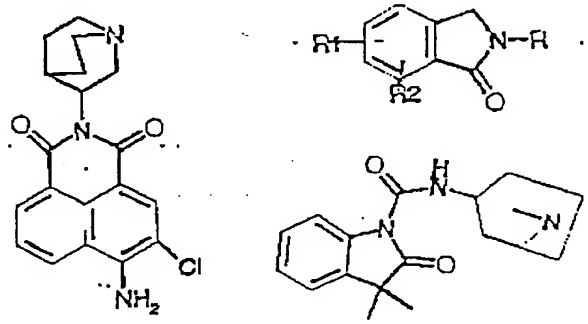
SB 204070

the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone



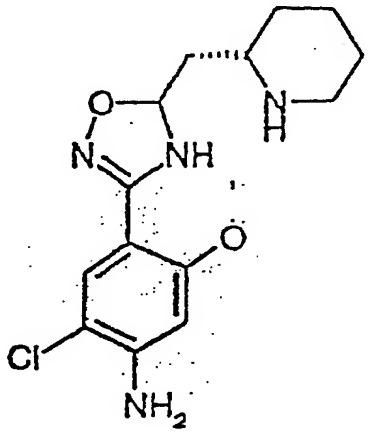
e.g. preferably RS 67333 and RS 17017;

naphtalimides, preferably RS 56532;



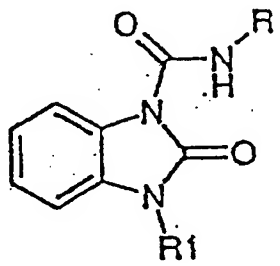
benzindolones;

compounds in which the amide fuction has been replaced with an oxadiazol ring;



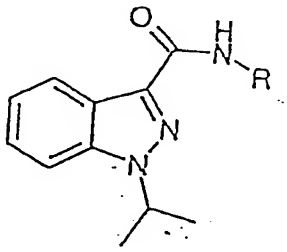
preferably YM-53389;

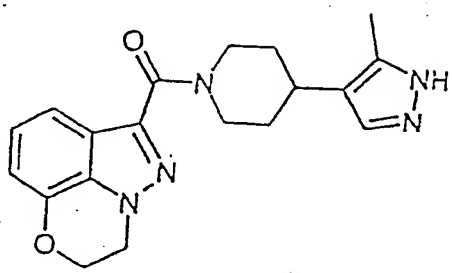
benzimidazolone-1-carboxamides



preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

the carboamides

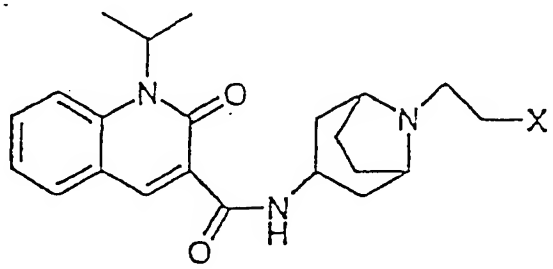




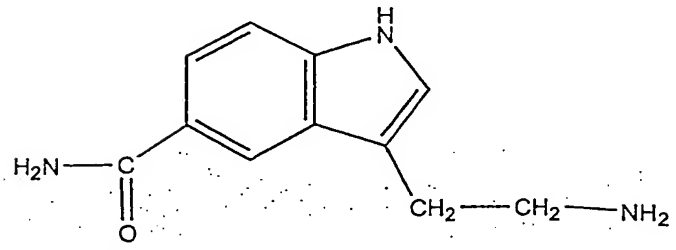
indols, preferably 5-methoxytryptamine, 2-methyl-serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side chain:

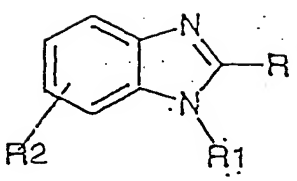
benzokinolinones



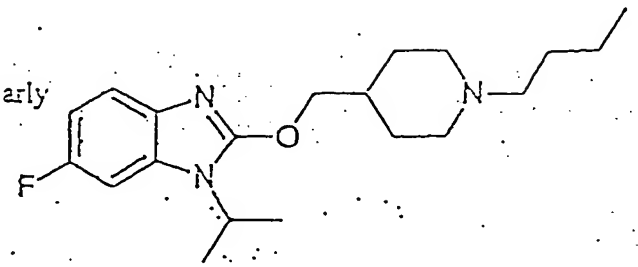
5-carboxamidotryptamine (5-CT), with the structural formula:



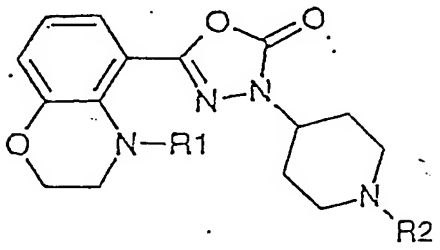
3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,



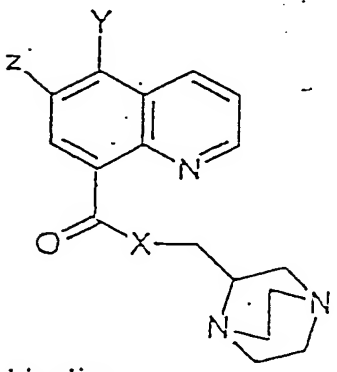
, particularly



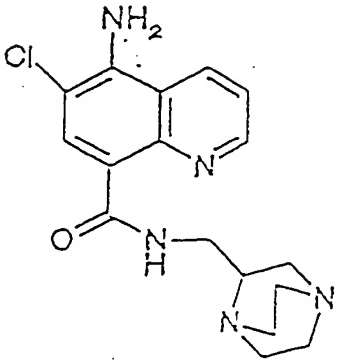
2-piperidinmethylethers of bensimidazol



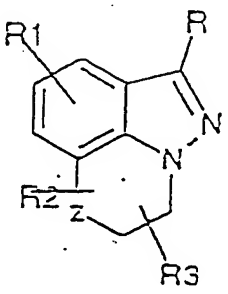
oxadiazalon based substance



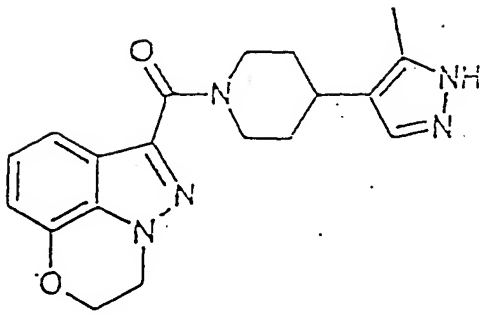
, particularly

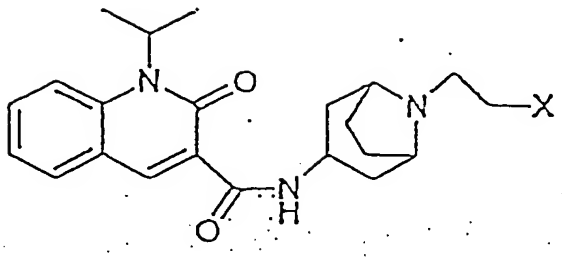


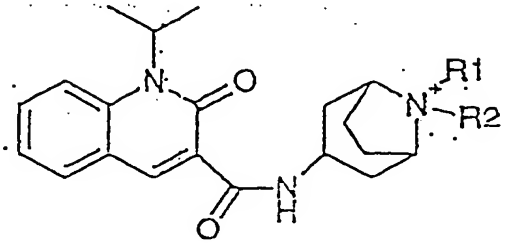
kinolines



, particularly







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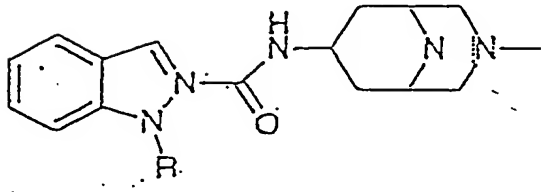

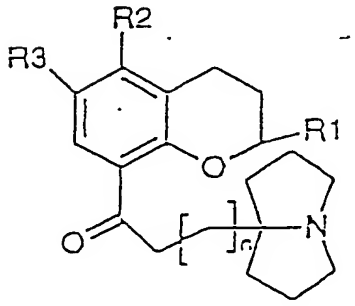

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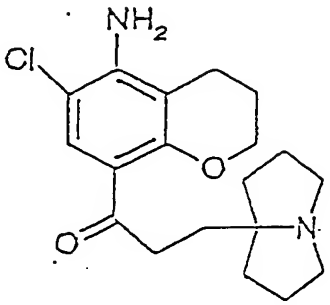
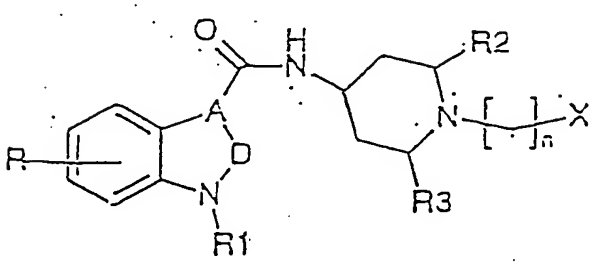
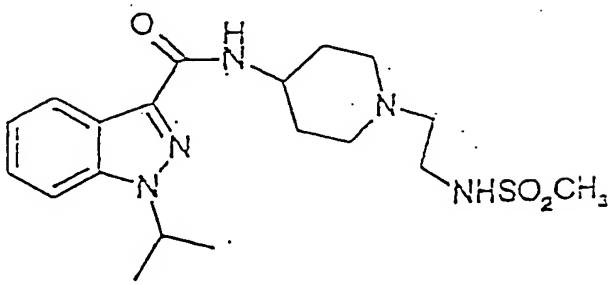


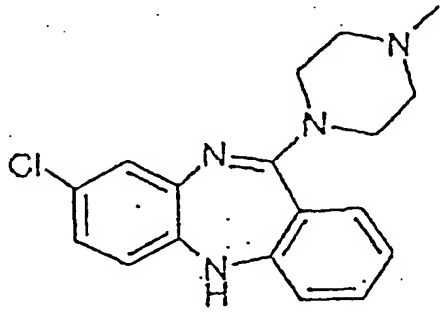
benzopyranes



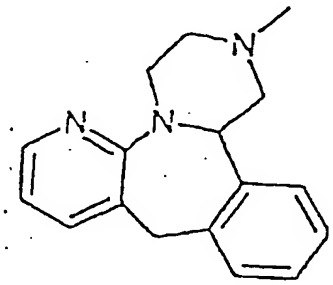


and serotonin (5-HT) and derivatives and pharmaceutically acceptable salts thereof.

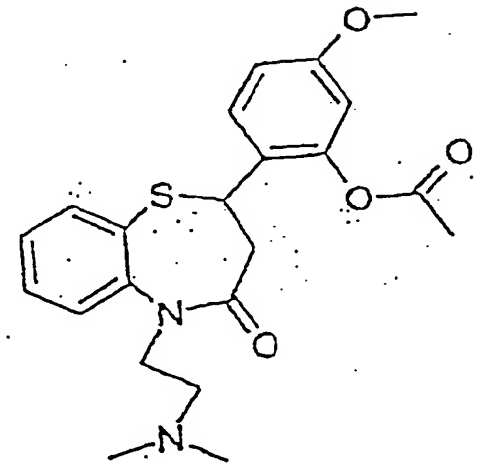
b) 5-HT_3 receptor antagonists:



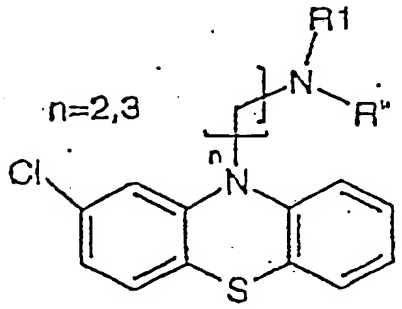
benzazepines, preferably mirtazapine



benztiazephines, preferably diltiazem

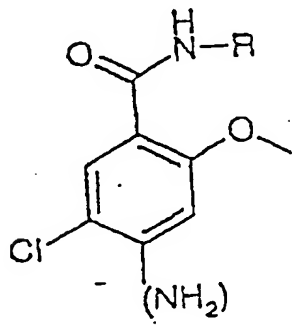


and fentiazines



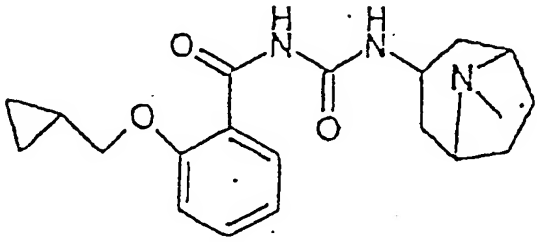
preferably perphenazine, stemetil;

compounds also having 5-HT_4 receptor agonist activity, preferably benzamides



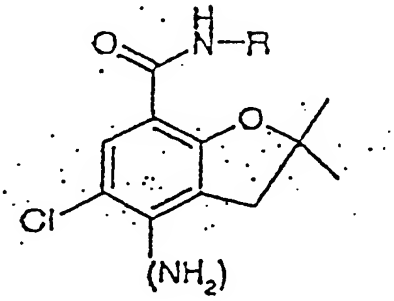
(cisapride, zacopride, mosapride, pancropride, BRL 24924, BMY 33462)

and



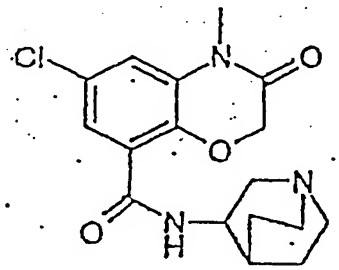
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



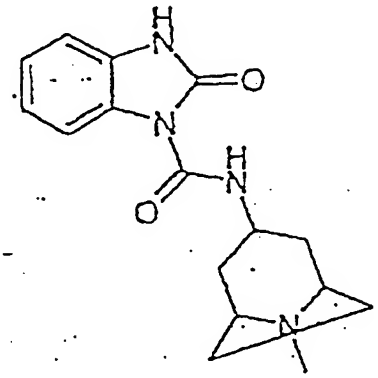
(preferably zatosetron=LY 277359, ADR 851);

1,4-bensoxazin-8-carboxamides



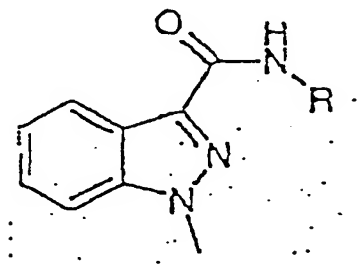
preferably azasetron (=Y25130);

benzimidazolones



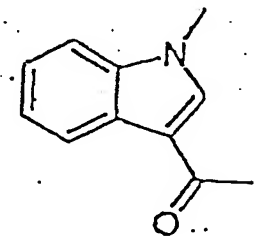
preferably itasetron (=DAU 6215);

indazol-3-carboxamides

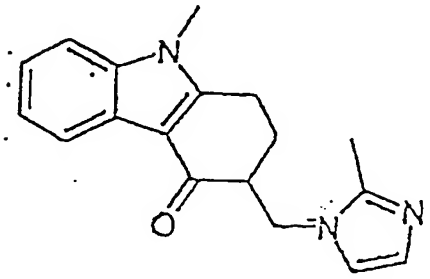


preferably N 3389, LY 278584, DAT 582;

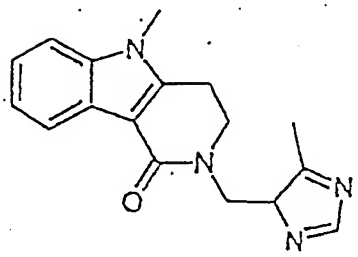
wherein the latter group reminds most of the specific 5-HT_3 antagonists, which contains the group



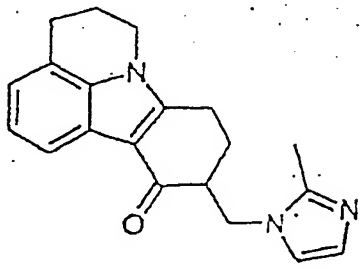
in different forms, such as



ondansetron

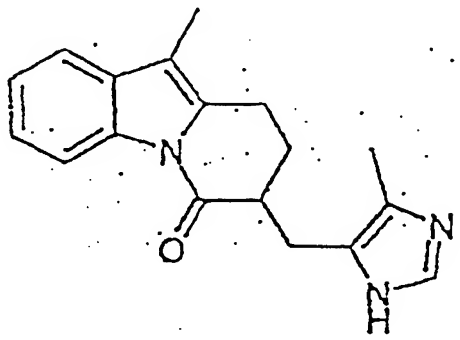


alosetron



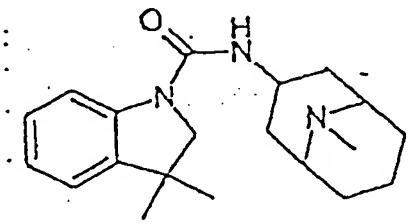
cilansetron

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen



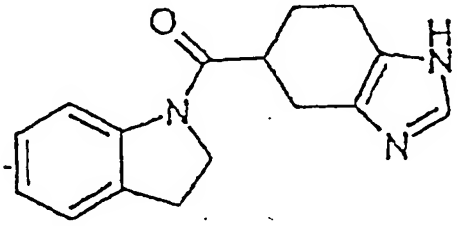
FK 1052

also being an antagonist against both 5-HT_3 and 5-HT_4 receptors,



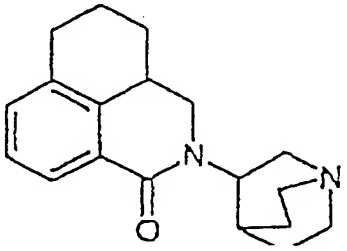
BRL 46470 A

bisindoles

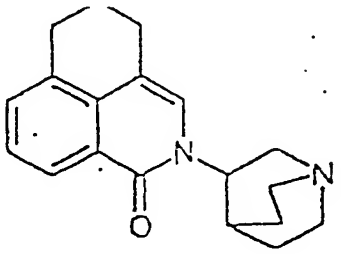


YM 114

isoquinoline-1-ones

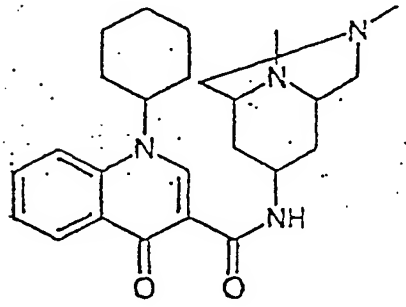


palonosetron (=RS 25259-197)

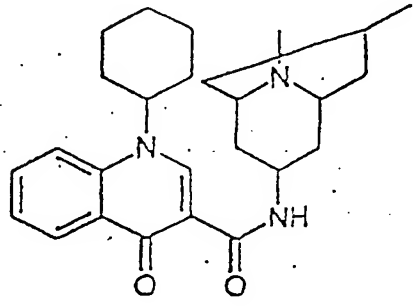


RS 42358-197

and the quinoline-3-carboxamides

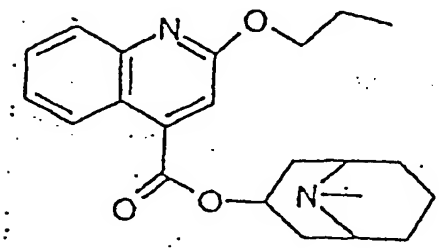


WAY-SEC 579

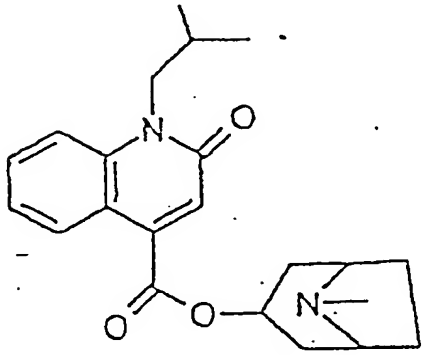


Mirisetron (=WAY 100579),

quinoline-4-carboxylates

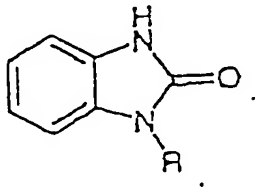


preferably KF 17643



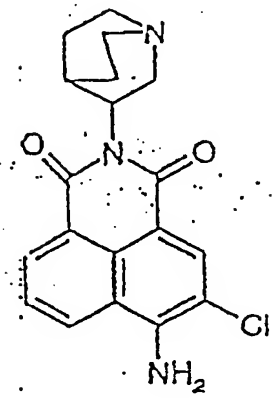
preferably KF 18259;

benzimidazolones



preferably itasetron (DAU6215),

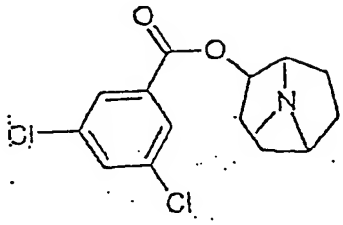
and the naphtimides



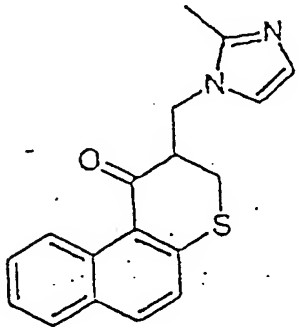
RS 56532

preferably RS 56532;

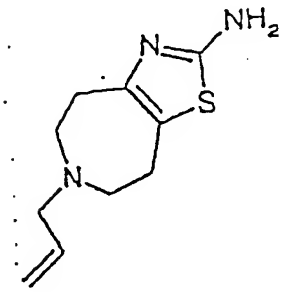
MDL 72222, which also is a specific 5-HT_3 antagonist;



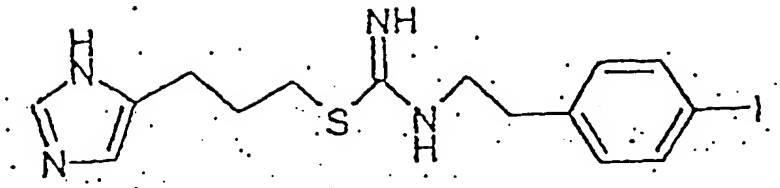
; and



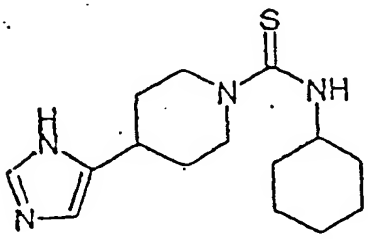
GK 128



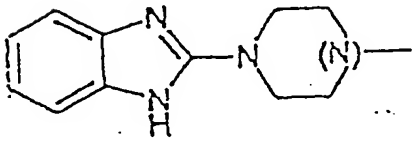
Talipexole



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide,

Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect, and derivatives and pharmaceutically acceptable salts thereof.

11. Use according to claim 10, wherein the composition comprises the following combinations of a 5-HT_4 receptor agonist and a 5-HT_3 receptor antagonist: VB20B7 and Tropanyl 3,5-dimethylbenzoate, VB20B7 and MDL 72222, RS67333 and Tropanyl 3,5-dimethylbenzoate, RS76333 and MDL 72222, VB20B7 and ICI 169369, RS67333 and ICI 169369, Zacopride and Tropanyl 3,5-dimethylbenzoate, Zacopride and MDL 72222, RS56532 and Tropanyl 3,5 dimethylbenzoate, RS56532 and MDL 72222, Itasetron and Tropanyl 3,5-dimethylbenzoate, Itasetron and MDL 72222, VB20B7 and SDZ 216-525, and RS67333 and SDZ 216-525.

12. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a composition according to any one of claims 10 and 11.

13. A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease,

wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a 5-HT_4 receptor agonist according to any one of claims 1 and 2 and a 5-HT_3 receptor antagonist according to any one of claims 5 and 6, either simultanoeously or sequentially.

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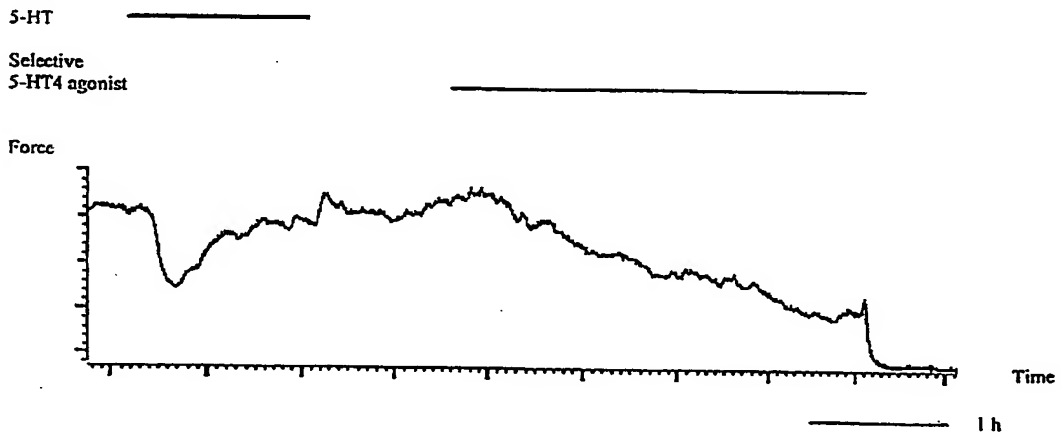
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RECEPTOR AGONISTS AND ANTAGONISTS



(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

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RECEPTOR AGONISTS AND ANTAGONISTS

Field of the Invention

The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

Background of the Invention

Receptors of the 5-HT (serotonin; 3-(β-aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in *e.g.* WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT_1 type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., *Eur. J. Pharm.*, **334**, 1-23 (1997), which is incorporated herein by reference.

A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference.

SU 1 701 320 A1 discloses the use of serotonin for treatment of acute asthma attacks. This reference does not suggest any receptor mechanism for serotonin, which is a compound with both a contracting and a relaxing effect on the airways, as is further discussed herein below.

In the RBI Handbook or Receptor Classification and Signal Transduction, 3rd Edition, 1998, RBI, One Strathmore Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling are compounds having agonist or antagonist activity to various receptors disclosed.

Disclosure of the Invention

The present invention is based on the novel finding that certain 5-HT receptors are of utmost importance in regulating bronchocontraction. In summary, it is disclosed herein that compounds having agonist activity to the 5-HT_4 receptor bring about a bronchorelaxing action upon administration thereof, and are therefore suitable as agents for treatment of bronchocontraction disorders. It is also disclosed herein that compounds having antagonist activity to the 5-HT_3 receptor, are suitable agents in the treatment of bronchocontraction disorders. Methods for treatment of bronchocontraction disorders are also disclosed.

As used herein, the expression bronchocontraction disorder refers to an abnormal increase of the force development of the smooth muscle, resulting in a reduced diameter in some or all of the airways of the lungs and/or the extrapulmonary airways. Said expression also refers to reduction of airflow caused by swelling, oedema, plasma extravasation or mucous secretion caused by *e.g.* asthma or any other disorder related thereto.

Accordingly, the present invention relates, in one of its aspects, to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic

treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

The present invention also relates, in another aspect, to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

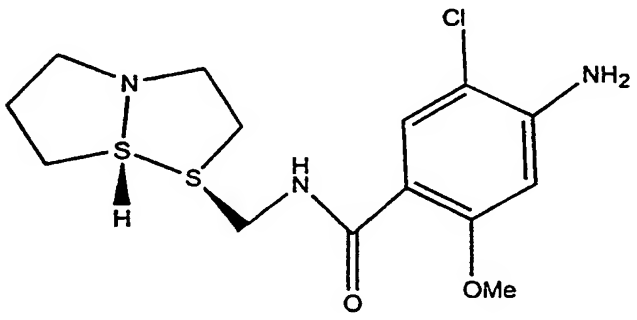
Said bronchocontraction may also occur in conjunction with such disorders as *e.g.* emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions, including schizophrenia.

The present invention also relates to the use of a compound having antagonist activity to a 5-HT_3 receptor in combination with a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders in-

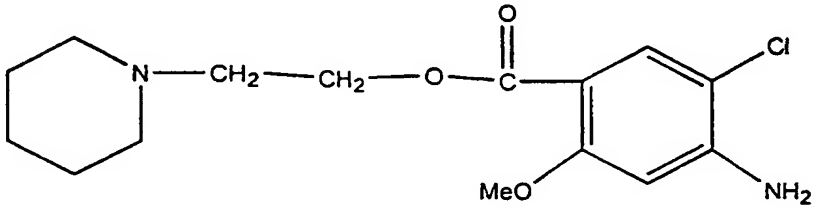
volving bronchocontraction. In a preferred embodiment said compound having agonist activity is serotonin or a derivative thereof having agonist activity to the 5-HT_4 receptor. This combination of the 5-HT_3 receptor antagonist and the agonist increases the beneficial effect of serotonin, particularly in the presence of a serotonin uptake inhibitor (SRI). Further, the compounds having agonist activity to the 5-HT_4 receptor to be used according to the present invention are also useful in the present combination embodiment. In particular, said medicament is intended for treatment of asthma and disorders related thereto.

According to the present invention several known substances are able to stimulate the 5-HT_4 receptor, without activating the contracting 5-HT_3 receptor, thereby, surprisingly, generating a relaxing effect on the bronchocontraction. Such agonist compounds are selected from the group comprising the substances SC 53116, ML 10302, RS 67506 and BIMU 8, which are defined below, as well as the more unspecific 5-carboxamidotryptamine, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same relaxation effect.

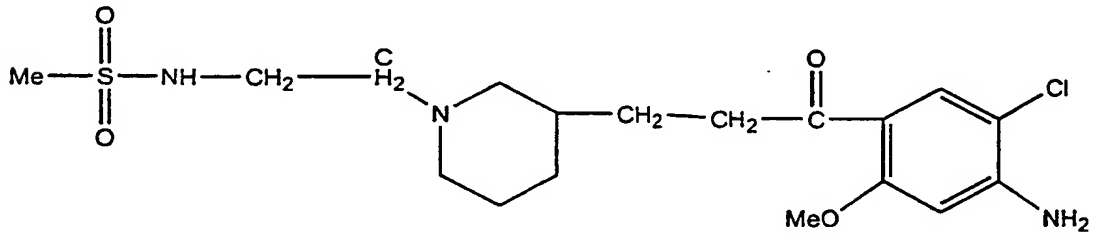
The invention also relates to the use of one or more of the above-mentioned agonist compounds: SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



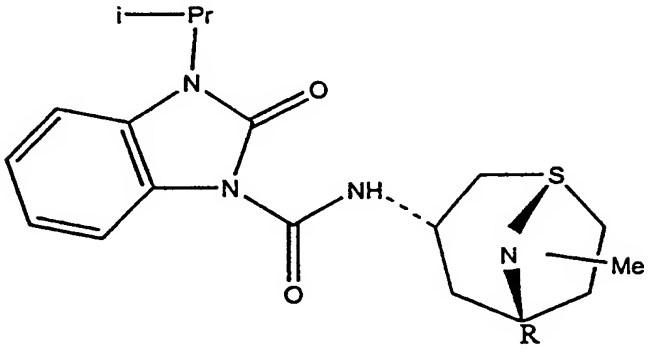
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



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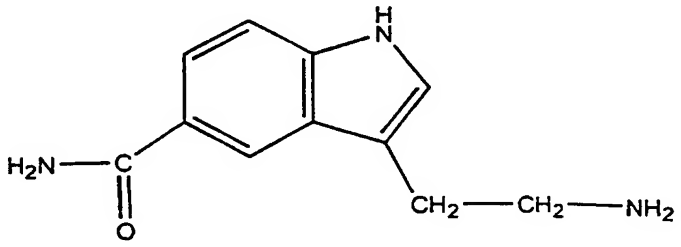
5-carboxamidotryptamine (5-CT), having the structural formula:



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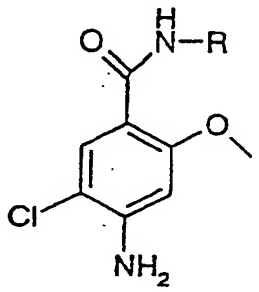
ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimetyltryptamin, 3-Me-8-OH-DPAT, ML-1035,
15 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253
20 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod) and derivatives and pharmaceutically acceptable

salts thereof having essentially the same relaxing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the bronchocontraction by at least 30%, preferably at least 60%, most preferably at least 90%.

Most of the different 5-HT_4 agonists can be divided in certain groups, wherein each group contains a common structural element. The largest group, and also the basis for several others, are the benzamides. They all contain the structural element 4-amino-5-chloro-2-methoxy benzamide and are further developments of the first 5-HT_4 agonist, metoclopramide.



These compounds are also potent 5-HT3-antagonists:

- 3-(4-Allylpiperazin-1-yl)-2-quinoxalinecarbonitrile
- 5-[(Dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole
- 3-(1-Piperazinyl)-2-quinoxalinecarbonitrile
- Granisetron
- RS-25259-197
- SEC-579, Mirisetron
- SC-52491
- KB-6933
- BRL 46470, Ricasetron
- Lerisetron
- KAE-393/YM-114
- AS-5370
- DAT-582
- N-3256
- SDZ 214-322
- KF-20170
- Lurosetron
- Galdansetron
- ONO-3051
- CP-93318
- Batanopride
- GR 67330
- SDZ 206-830
- QICS 205-930
- BRL 24682
- LY 258-458
- Zacopride, S(-)Zacopride, R(+)Zacopride
- RP 62203
- SDZ 206-792
- BRL 47204
- SDZ 210-204
- LY-211-000
- MCPP
- MK 212
- Mianserin
- SDZ 210-205

- Bufotenine
- Pitozifen
- Indalpine
- Cizapride
- Cyproheptadine
- 2-Methyl-5HT
- Amitriptyline
- LY 278-989
- Imipramine
- Phenylbiguanide
- TFMPP
- 5,7-DHT
- RU 24969
- Ritanserin
- NAN-190
- Mepyramine
- Metergoline
- Methysergide

These compounds are also potent 5-HT4-agonists:

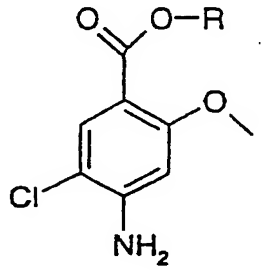
- Bufotenine
- 5-MeO-N,N,DMT
- GR 113,808
- α-Metyl-5HT

Another common feature is a basic nitrogen in a side chain from the amide nitrogen. This basic nitrogen is often a part of a sterically locked system. Examples of substances from this group are:

BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, TKS 159, Y-34959, YM-09151, YM-47813, Zacopride.

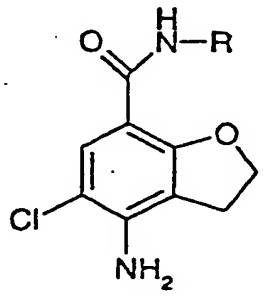
Thus, a structure-activity relation study performed indicates that a benzene ring and a basic nitrogen in the same plane as the ring and at a distance of 8±1 Å from the center of the benzene ring is required. The nitrogen should be locked in that position with a view to obtaining selectivity against other 5-HT receptors. A lipophilic group on the basic nitrogen also seems to be important for the agonistic action. Further, a heteroatom having a free electron pair close to the indole nitrogen in tryptamine seems to give a positive effect.

Benzoic acid esthers are modifications of the benzamide theme:

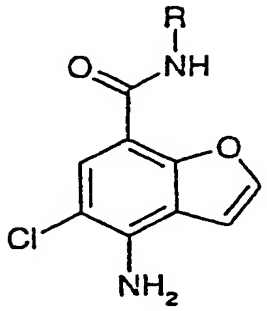


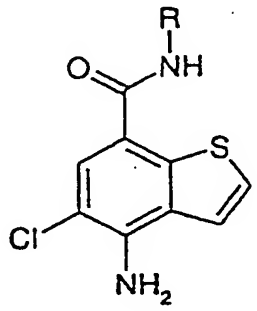
The only difference is that the amide group has been replaced with an esther group. Examples are ML 10302, RS 57639, and SR 59768.

Another variant of the basic theme is to introduce the methoxy group into a ring, thereby arriving at a 2,3-dihydro-bensofuran-7-karboxamide group. Examples are ADR 932, Prucalopride (=R 093877); and SK-951.

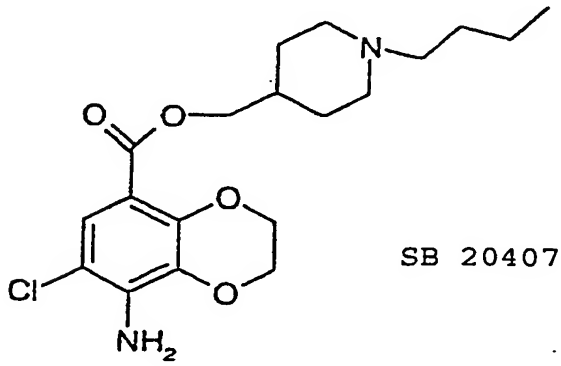


Benzofuranes and benzotiophenes are also contemplated,



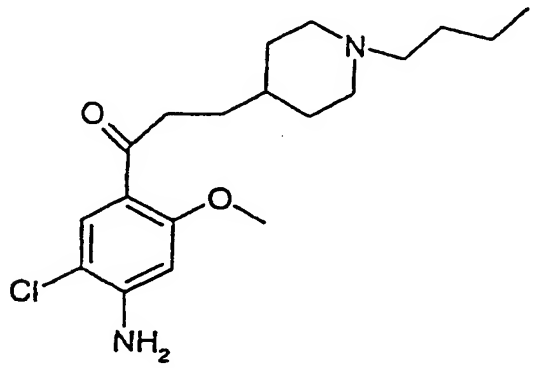


as well as the benzodioxan



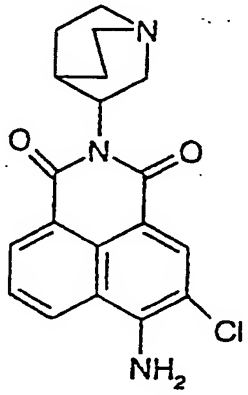
SB 204070

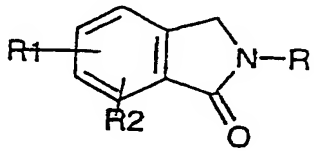
Still another variant is based on the discovery that the benzoic acid antagonist RS 23597 (an esther) was transformed to an agonist if it was converted to a ketone

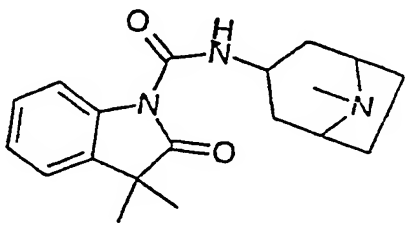


, e.g. RS 67333 and RS 17017.

The basic concept also applies for naphtalimides, e.g. RS 56532.

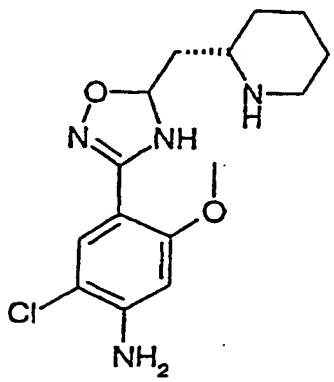






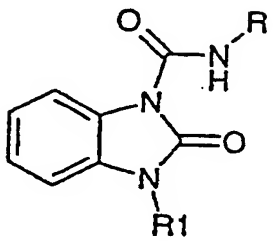
Benzindolones are also contemplated

The amide fuction may also be replaced with an oxadiazol ring.



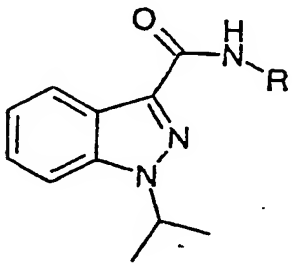
, e.g. YM-53389

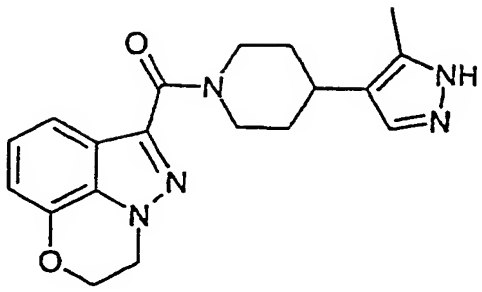
Benzimidazolone-1-carboxamides



, e.g. BIMU 1, BIMU 8, DAU 6215, and DAU 6236, are also contemplated.

The carboamides

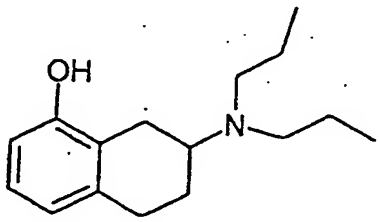




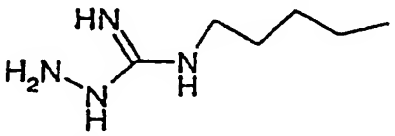
are also contemplated.

Some indols are olso useful as 5-HT_4 agonists, e.g. 5-methoxytryptamine, 2-methylserotonine, and 5-hydroxy-N,N-di-methyltryptamine.

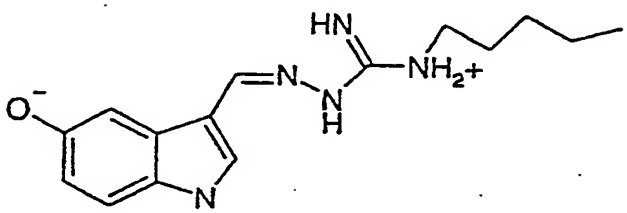
Other tested substances useful as 5-HT_4 agonists according to the present invention are



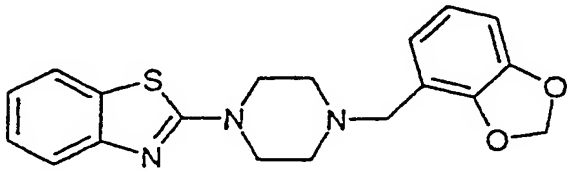
SDZ 216-454



Zelmac=SDZ HTF 919



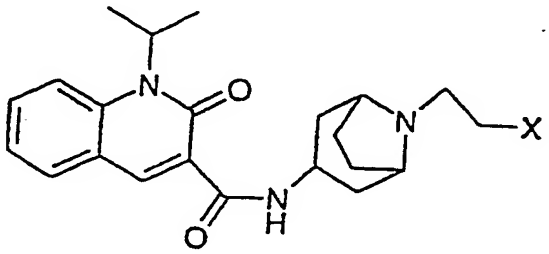
VB20B7



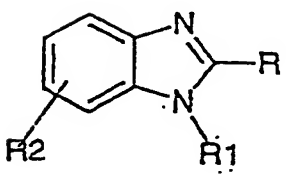
It should be noted that many of these substances may be quaternized on the nitrogen in the side chain without losing the activity.

The most active agonist at present seems to be Zelmac.

Benzokinolinones



Further 5-HT4 agonist structures useful according to the present invention



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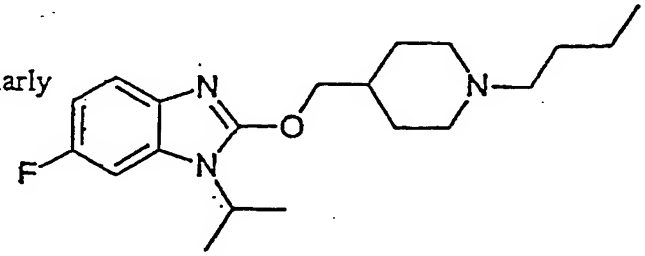
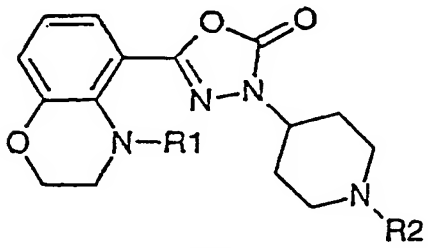


2-piperidinmethylethers of bensimidazol

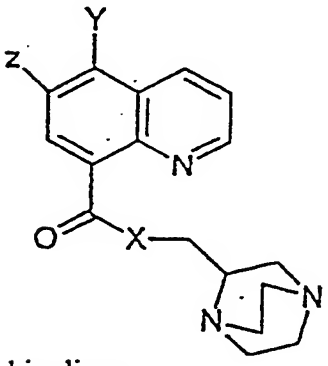


oxadiazalon based substance

Arylcarbamate derivatives of 1-piperidineethanol
4-amino-5-chloro-2methoxybenzoic acid esters,
e.g. ML10302, RS 57639 and SR59768

4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide,e.g. TKS159

thiophene carboxamide derivatives 3 (a-j)
5. Azabicyclo(x.y.z) derivatives
2-piperazinylbenzoxazole derivatives
2-piperazinylbenzothiazole derivatives, e.g. VB20B7
clebopride
Sandoz compound 1b



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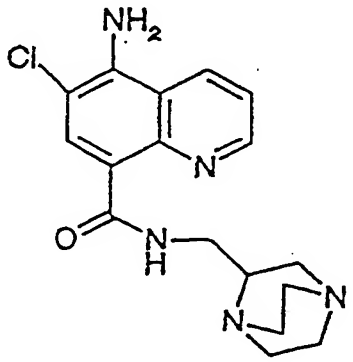
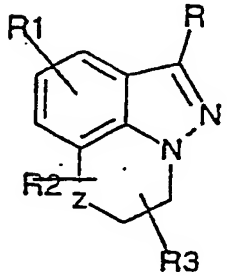


kinolines



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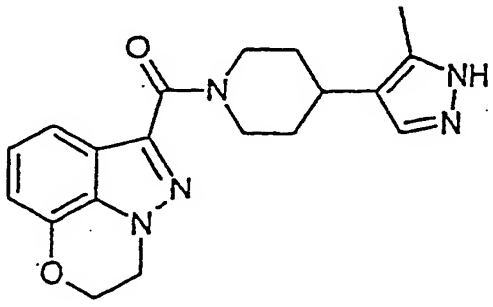

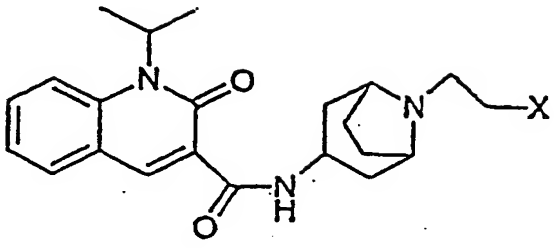

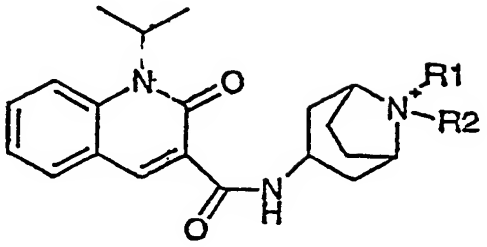

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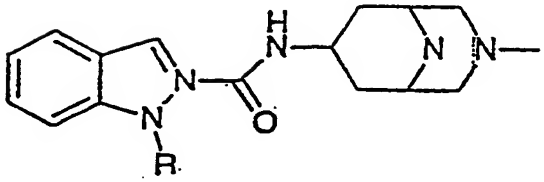

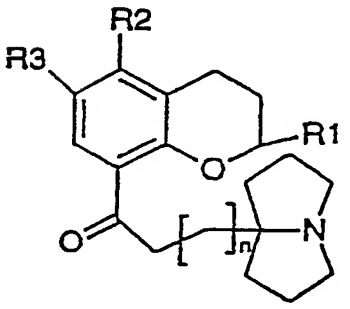

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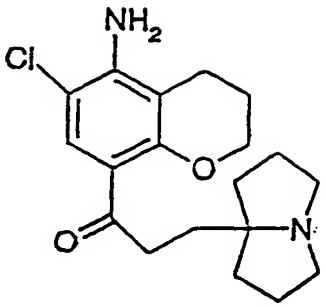
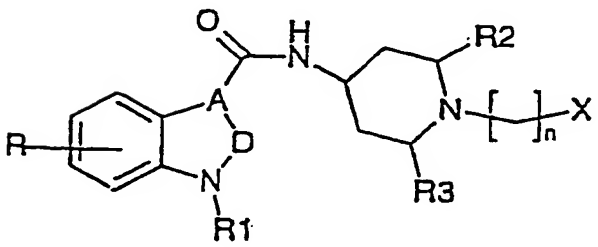
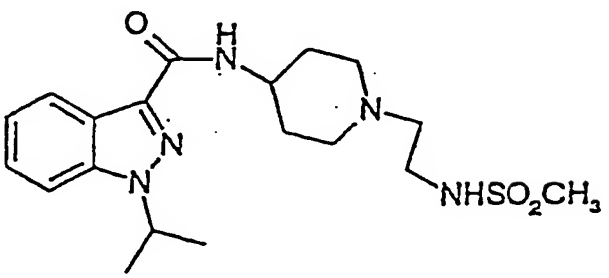


bensopyranes





The most preferred 5-HT_4 receptor agonist is RS 67333.

According to the present invention several known antagonist compounds are, surprisingly, able to influence the 5-HT_3 receptor, thereby generating a contraction reducing effect, i.e. a relaxation effect, and are selected from a group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Azasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=(R)AS-5370), Diltiazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICI 169369, ICS 205-930, Ifenprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine, LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochlorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915, RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Trifluoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359) and pharmaceutically acceptable salts thereof having the same or essentially the same contraction reducing effect.

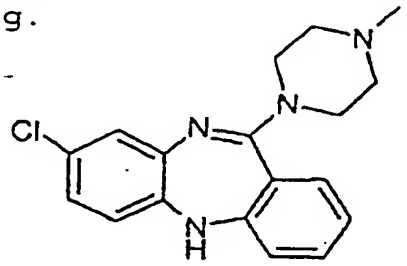
The present invention also relates to the use of one or more of the above-mentioned 5-HT_3 antagonist compounds and to derivatives and pharmaceutically acceptable salts thereof having essentially the same contraction reducing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving

bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

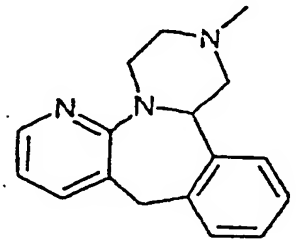
The 5-HT_3 receptor is a ligand modulated ion channel. The known anxiety repressing bensodiazepines influence not only 5-HT_3 but also several other receptors for different neurotransmittors. Several potent specific 5-HT_3 antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial pharmaceuticals, however, not against disorders involving bronchocontraction.

Some of the 5-HT_3 receptor antagonists are at the same time 5-HT_4 receptor agonists. However, for a substance to be active as a 5-HT_3 receptor antagonist, the distance from the aromatic center to the basic nitrogen should be about 7,5 Å and no large substituents are tolerated on the basic nitrogen. In contrast, for 5-HT_4 receptor agonists the corresponding distance is about 8 Å, and a large lipophilic group may be bound to the basic notrogen, thereby obtaining a better binding to 5-HT_4.

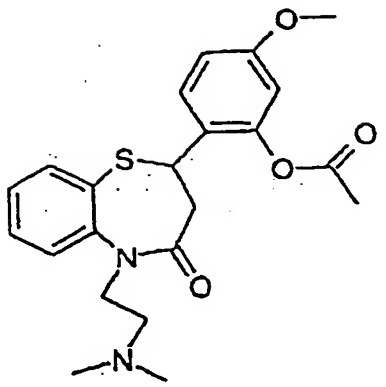
The 5-HT_3 antagonist may be divided in certain classes with the basis on the chemical structure. Some are unspecific, e.g.



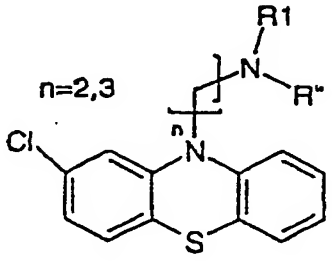
benzazepines, e.g. mirtazapine



benztiazephines, e.g. diltiazem

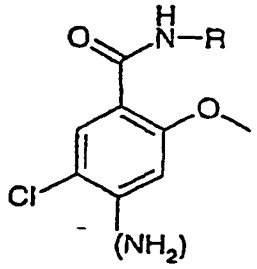


and fentiazines



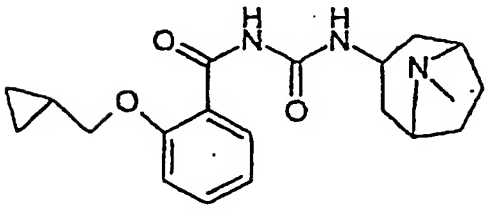
, e.g. perphenazine, chlorpromazine, stemetil

Some are 5-HT_4 agonists, e.g. benzamides



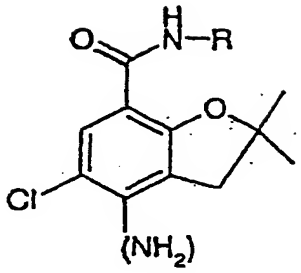
(cisapride, zacopride, mosapride, metoclopramide, pancropride, BRL 24924, BMY 33462)

and



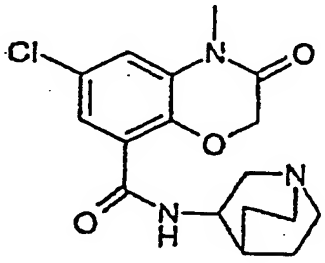
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



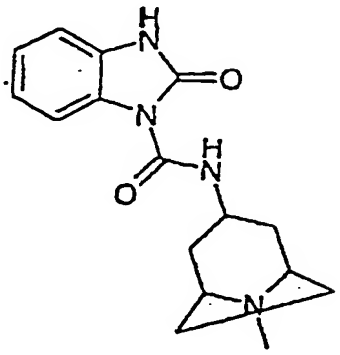
(e.g. zatosetron=LY 277359, ADR 851)

1,4-bensoxazin-8-carboxamides



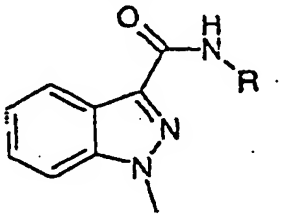
, e.g. azasetron (=Y25130)

benzimidazolones



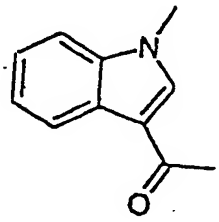
, e.g. itasetron (=DAU 6215)

indazol-3-carboxamides

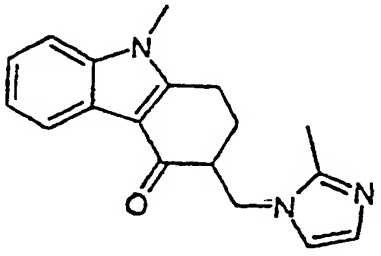


, e.g. N 3389, LY 278584, DAT 582

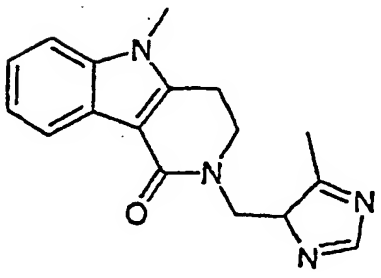
The latter group reminds most of the specific 5-HT_3 antagonists, which after contains the group



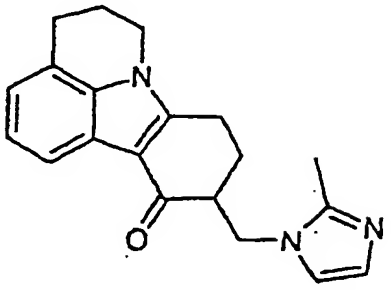
in different forms, such as



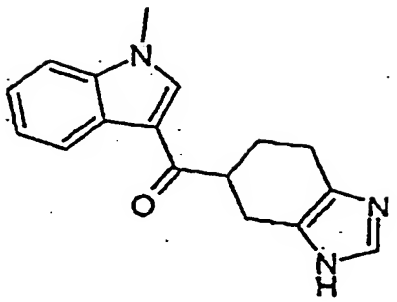
ondansetron



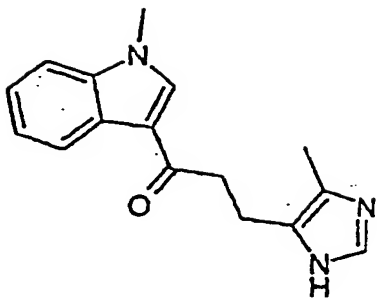
alosetron



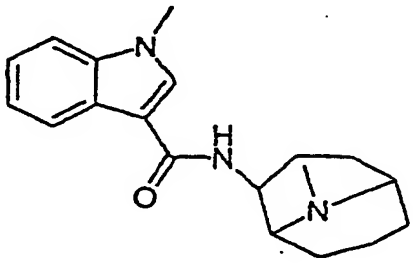
cilansetron



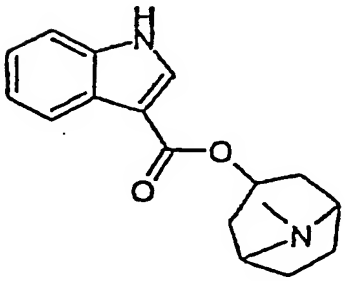
ramosetron



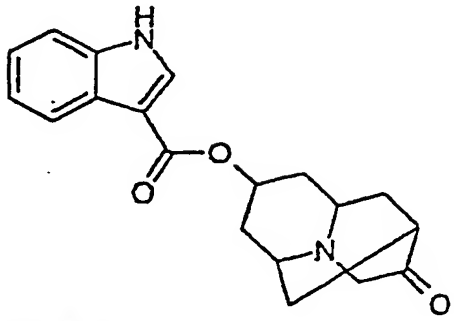
GR 65630



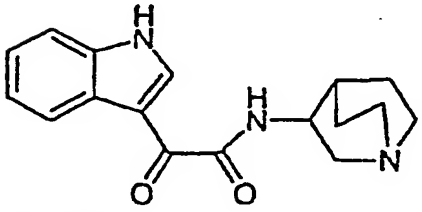
granisetron



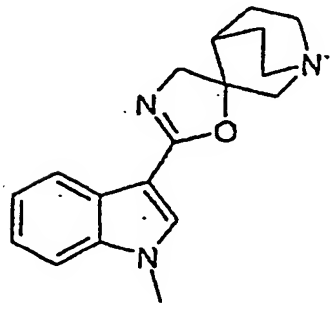
tropisetron



dolasetron

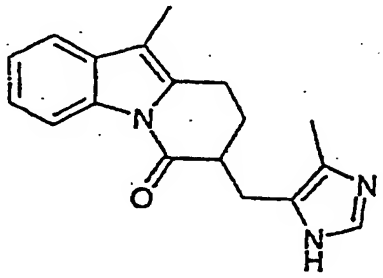


RS 56812



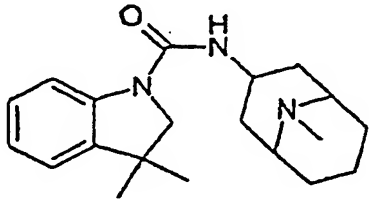
L 683877

In one group of substances the structure has been inverted and the carbonyl group has been placed on the indoline nitrogen



FK 1052

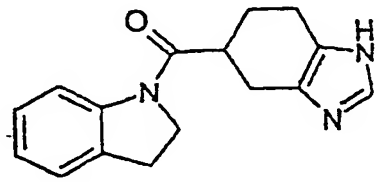
This substance is unique by being an antagonist against both 5-HT_3 and 5-HT_4.



BRL 46470 A

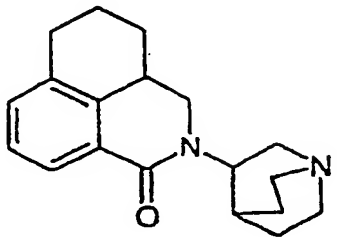
BRL 46470A binds to two different positions of the receptor.

A further development is the so-called bisindoles

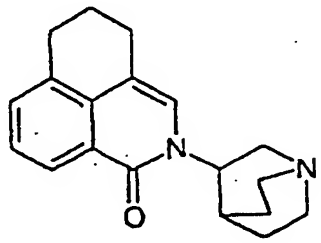


YM 114

Another group is the isoquinoline-1-ones

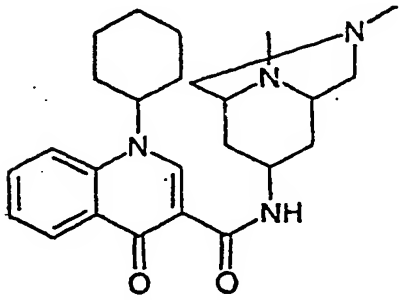


palonosetron (=RS 25259-197)

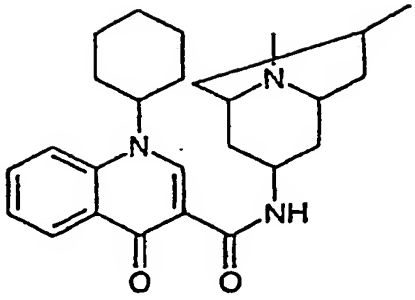


RS 42358-197

and the quinoline-3-carboxamides

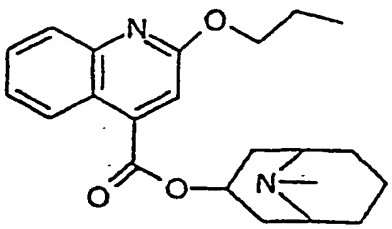


WAY-SEC 579

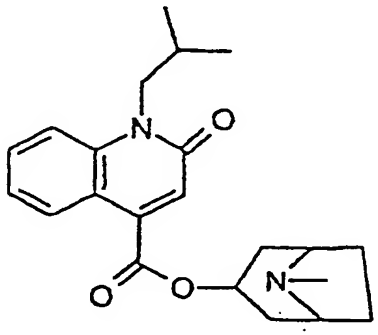


Mirisetron (=WAY 100579)

Also the quinoline-4-carboxylates are active antagonists

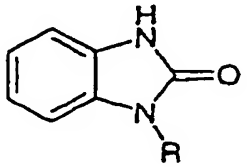


, e.g. KF 17643



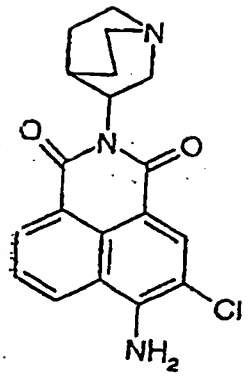
, e.g. KF 18259

Other compounds are benzimidazolones



e.g. droperidol (neurolidol, etc.), itasetron (DAU6215),

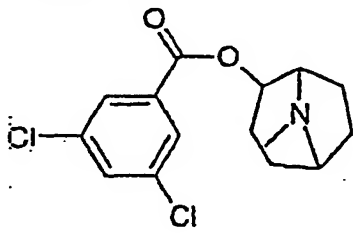
and the naphtimides



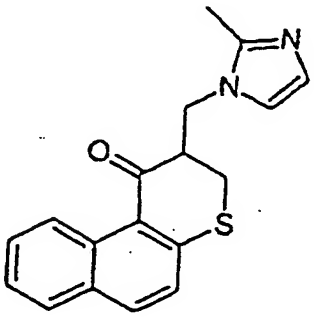
RS 56532

, e.g. RS 56532

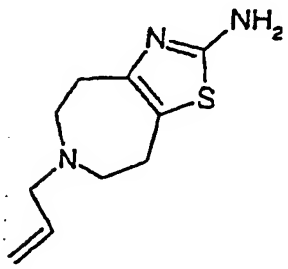
A unique single structure is MDL 72222, which also is a specific 5-HT_3 antagonist



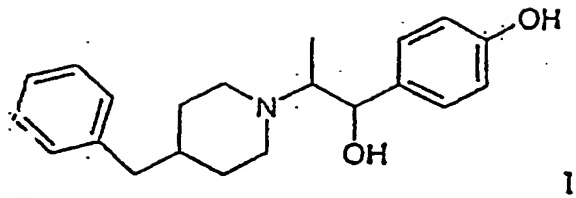
Other specific structures are



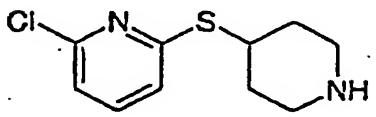
GK 128



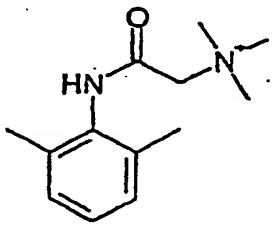
Talipexole



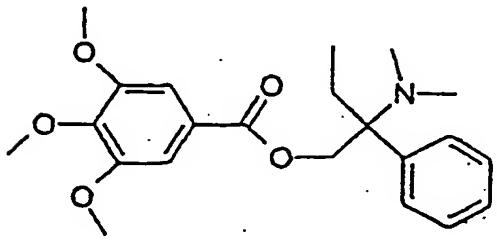
Ifenprodil



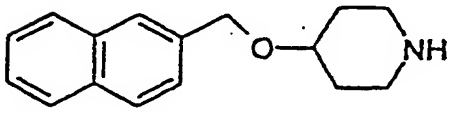
Anpirtoline



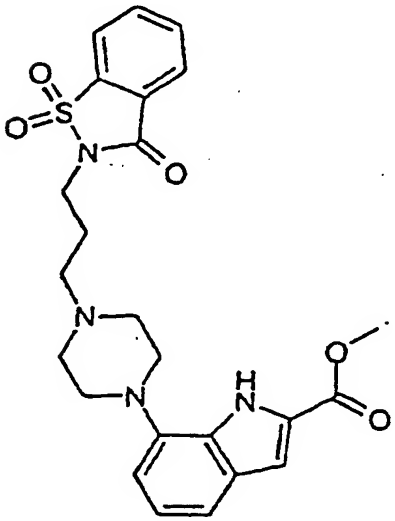
QX 222



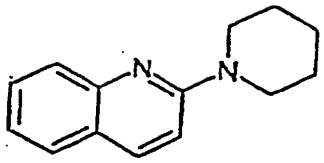
Trimebutine



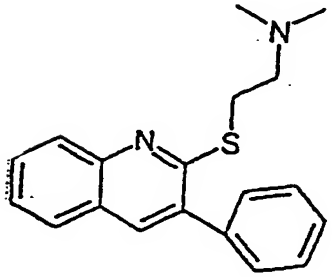
Litoxetine



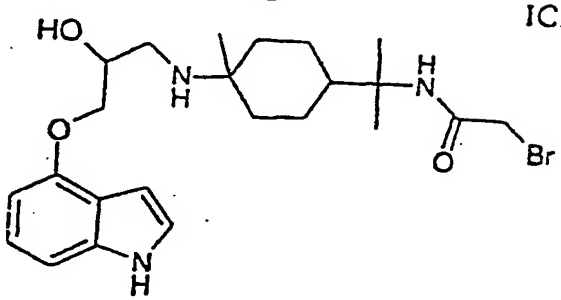
SDZ 216-525



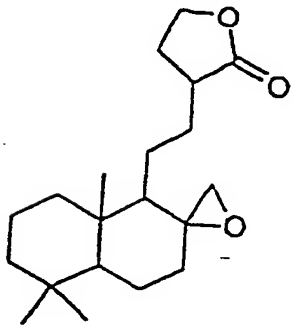
Quipazine



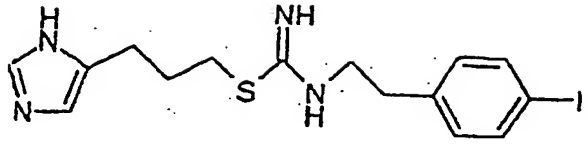
ICI 169369



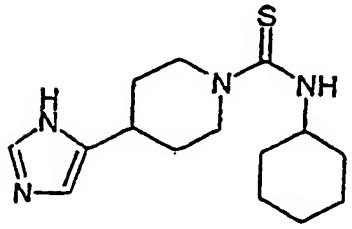
BIM



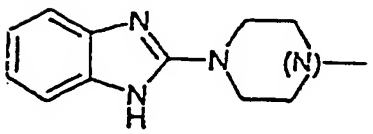
Galanolakton



iodophenpropit



thioperamide, and



2-piperidin- and 2-piperazin-benzimidazoles.

The most preferred 5-HT_3 receptor antagonist is tropanyl-3,5-dimethylbenzoate.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of the compound according to the present invention having agonist activity to the 5-HT_4 receptor. Preferably, said method relates to the treatment of asthma and disorders related thereto.

The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to the present invention having antagonist activity to a 5-HT_3 receptor. Preferably, said

method relates to treatment of asthma and disorders related thereto.

Further, the present invention relates to a method for treatment of disorders involving bronchocontraction, wherein the above-mentioned combination of agonist(s) and antagonist(s) is administered.

The expression "has the capacity of reducing the pathological bronchocontraction by at least ….%" used throughout the present patent application means that the compound in question reduces the contraction in the airways caused (1) either by the underlying disease (asthma etc) or (2) by the administration of 5-HT or other substances with 5-HT_3-activating properties. The level of contraction in the airways can, for instance, be determined by spirometric measurements of the Forced Expiratory Volume (FEV1), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT_4 receptor, this sustained relaxing effect is achieved because the contractile 5-HT_3 receptor is not affected; only the relaxing 5-HT_4 receptor is activated. In the case of antagonists to the 5-HT_3 receptor, this effect is achieved due to direct blocking of the 5-HT_3 receptor, whereby the unspecific agonists to the 5-HT_4 receptor, such as 5-HT, can act without also causing contraction by the 5-HT_3 receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may optionally include two or more of the above outlined compounds.

Further, in the embodiment when the compound having 5-HT_3 antagonist activity is administered, optionally together with complementary serotonin or derivatives thereof, a serotonin uptake inhibitor can be added with a view to amplifying the relaxing effect.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Moreover, said medicament is preferably administered via the respiratory tract in the form of *e.g.* an aerosol or an air-suspended fine powder. However, in some cases a useful alternative to administration via the respiratory tract may be oral, topical, parenteral, subcutaneous, transdermal or rectal administration, wherein *e.g.* tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories are utilized.

Brief Description of the Drawing

Fig. 1 depicts the effects of 5-HT and the selective 5-HT_4 agonist RS 67333 on the spontaneous tone in human in vitro preparations. Note that 5-HT only gives a transient relaxation, while selective 5-HT_4 agonists give a strong sustained relaxing effect.

Detailed Description

The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in

the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead display a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin, also called 5-HT, which exerts agonist action on the receptors 5-HT_1, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 as well as on 5-HT_2 receptors.

Additional experiments have shown that when 1 µM serotonin was added to denuded airway smooth muscle preparations from the guinea-pig displaying a strong, smooth spontaneous tone, the average force level was increased significantly, *i.e.* a contraction was observed. A contractile effect of serotonin on airway smooth muscle has been reported in *e.g.* Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, **86**:789-798, 1999. However, when 10 µM of serotonin was added, the spontaneous tone was significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal level when the

preparations were again exposed to control conditions. Thus, it has now surprisingly been shown that serotonin brings about contraction of the airways at low concentrations and relaxation at high concentrations, consequently having a dual effect on the airways.

Furthermore, it has been shown that when the contracting 5-HT_{2a} receptor was blocked with ketanserin, the 5-HT, i.e. serotonin, induced almost no contraction, but instead only a significant relaxation. Similar experiments have also been performed on human in vitro preparations, from patients undergoing lobecotomy or pulmectomy due to lung cancer. It was found that in this tissue, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig. In human tissue, already 1 μM 5-HT induces a significant relaxation of the spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro preparations have shown that 5-HT indeed has a contractile component also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline. In guinea pig trachea, the contraction reaches a maximum after approximately 10 min, and this is followed by a considerable reduction of tone. However, human preparations instead induce a maximum relaxing effect after 5-10 min, which disappears gradually during the following 30-45 min (see Fig 1). The transient nature of the 5-HT relaxation is most likely caused by a simultaneous activation of the fast, relaxing 5-HT_4 receptor, and a slower activation of the contracting receptor, which in human airways surprisingly has been found to be the 5-HT_3 receptor. This is clear, because activation of the relaxing 5-HT_4 receptor by a substance that lacks 5-HT_3 receptor activating properties (such as RS 67333),

results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT or 5-HT analogues may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta2 receptor stimulation. However, from our experiments it seems clear that 5-HT is not effective or useful as the only treatment for e.g. asthmatic disorders, because of the transient relaxing effect by 5-HT (see Fig. 1). If instead, as we propose herein, a 5-HT analogue that lacks the 5-HT_3 activating properties is given, the relaxing effect is persistent, and not transient.

In summary, it has now been discovered that agonist action on the 5-HT_4 receptor results in a relaxing effect, whereas agonist action on 5-HT_3 receptors results in a contractile effect. In conclusion, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT_4 receptor as well as on the contracting 5-HT_3 receptor.

It was also deduced from these experiments that compounds having agonist activity to the 5-HT_4 receptor, while having only low or no agonist activity to a 5-HT_3 receptor, therefore are useful as agents for treatment of bronchocontraction disorders.

Thus, the present invention relates to the use of compounds having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament intended for treatment of bronchocontraction disorders, whereby said compounds have the strong bronchorelaxing effect of serotonin but have substantially no contractile effect. As mentioned above, the compounds used according to the present invention have only low or no agonist activity to 5-HT_3 receptors.

In the above mentioned experiments it has also been shown that compounds having antagonist activity to a

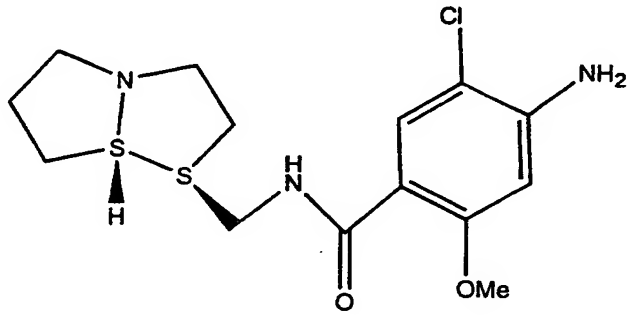
5-HT_3 receptor are useful as agents for treatment of bronchocontraction disorders, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT_3 receptor. The compounds according to the present invention having antagonist activity to the 5-HT_3 receptor may even be administered together with serotonin in the form of a complement to the serotonin content already present in the body with a view to obtaining an amplified contracting effect; or with any other substance having agonist activity to the 5-HT_3 receptor; or with a serotonin uptake inhibitor.

Said administration can be simultaneous or sequential, and a powerful relaxing effect on the bronchi can be achieved in this manner. Thus, the present invention also relates to the combined use of a compound having antagonist activity to a 5-HT_3-receptor and a compound having agonist activity to the 5-HT_4 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

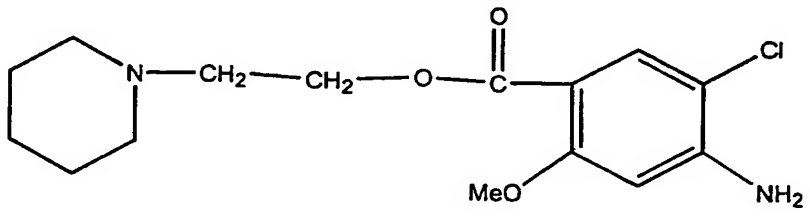
CLAIMS

1. Compound having agonist activity to a 5-HT_4 receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT_4 receptor for use as a medicament for treatment of disorders involving bronchocontraction.

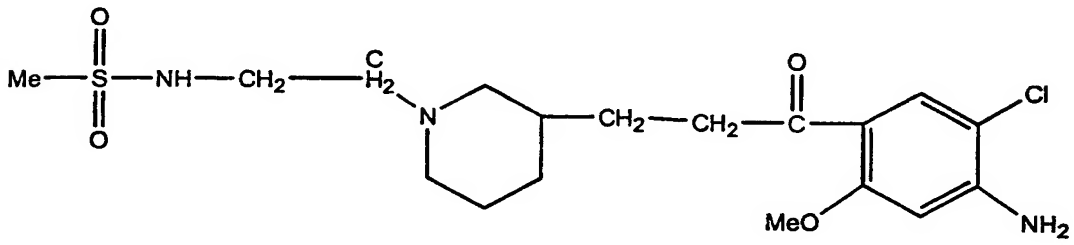
2. Compound according to claim 1, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



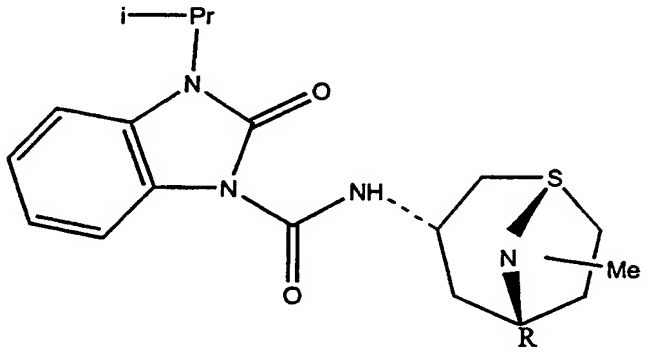
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



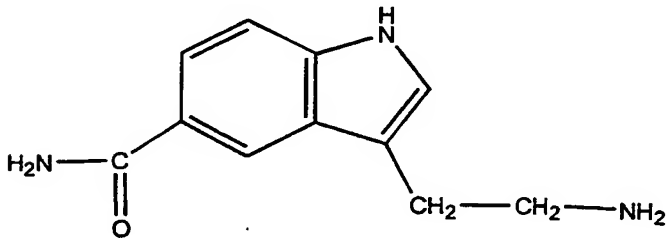
RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5-carboxamidotryptamine (5-CT), having the structural formula:

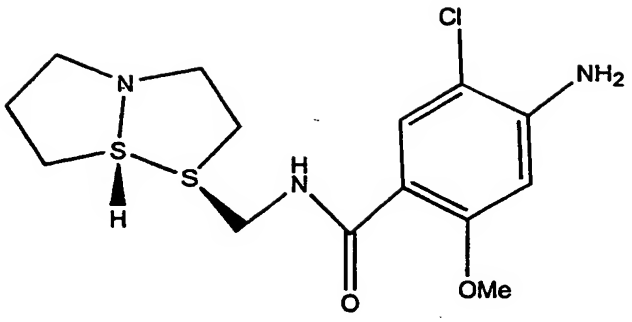


ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimetyltryptamin, 3-Me-8-OH-DPAT, ML-1035, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod).

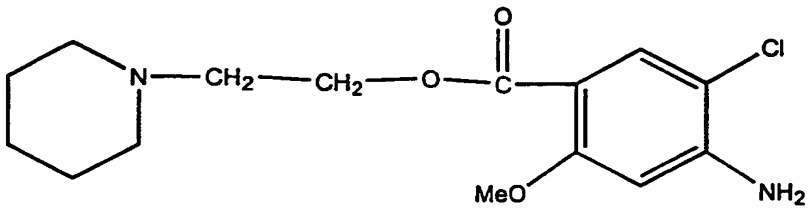
3. Compound according to claim 2, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

4. Use of one or more compounds according to claims 1 and 2 having agonist activity to a 5-HT_4 receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT_4 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

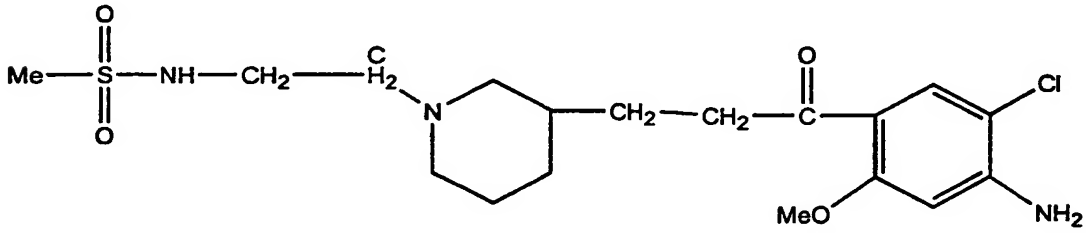
5. Use according to claim 4, wherein said one or more compounds has/have the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



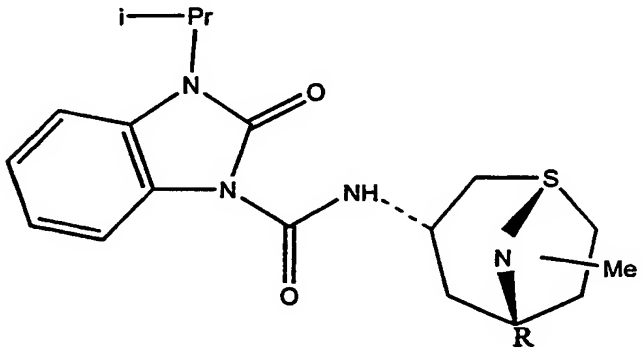
ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural formula:



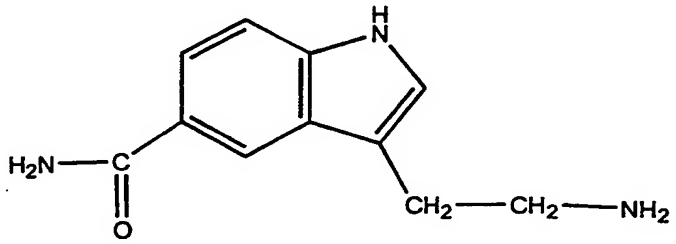
RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5-carboxamidotryptamine (5-CT), having the structural formula:



ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimetyltryptamin, 3-Me-8-OH-DPAT, ML-1035, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod).

6. Use according to claims 4 and 5, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

7. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claim 1.

8. Compound having antagonist activity to a 5-HT_3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor for use as a medicament for treatment of disorders involving bronchocontraction.

9. Compound according to claim 8, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Axasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=(R)AS-5370), Dilalazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICI 169369, ICS 205-930, Ifonprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine, LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochiorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915,

RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Tritiuoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359), preferably tropanyl-3,5-dimethylbenzoate.

10. Compound according to claim 9, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

11. Use of one or more of the compounds according to claims 8 and 9 and including ketanserin having antagonist activity to a 5-HT_3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_3 receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

12. Use according to claim 11, wherein said one or more compounds has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Axasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=(R)AS-5370), Dilalazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICI 169369, ICS 205-930, Ifonprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine,

LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochiorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915, RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Tritiuoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359), preferably tropanyl-3,5-dimethylbenzoate.

13. Use of one or more compounds according to claims 11 and 12 in combination, either simultaneously or sequentially, with a compound having agonist activity to the 5-HT_4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

14. Use according to claim 13, wherein said compound having agonist activity to the 5-HT_4 receptor is serotonin and derivatives thereof or a compound according to claims 1 and 2.

15. Use according to claims 11-14, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

16. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claims 11-14.

17. Composition comprising a combination of the compounds defined in claims 13 and 14 for use as a medicament for treatment of disorders involving bronchocontraction.

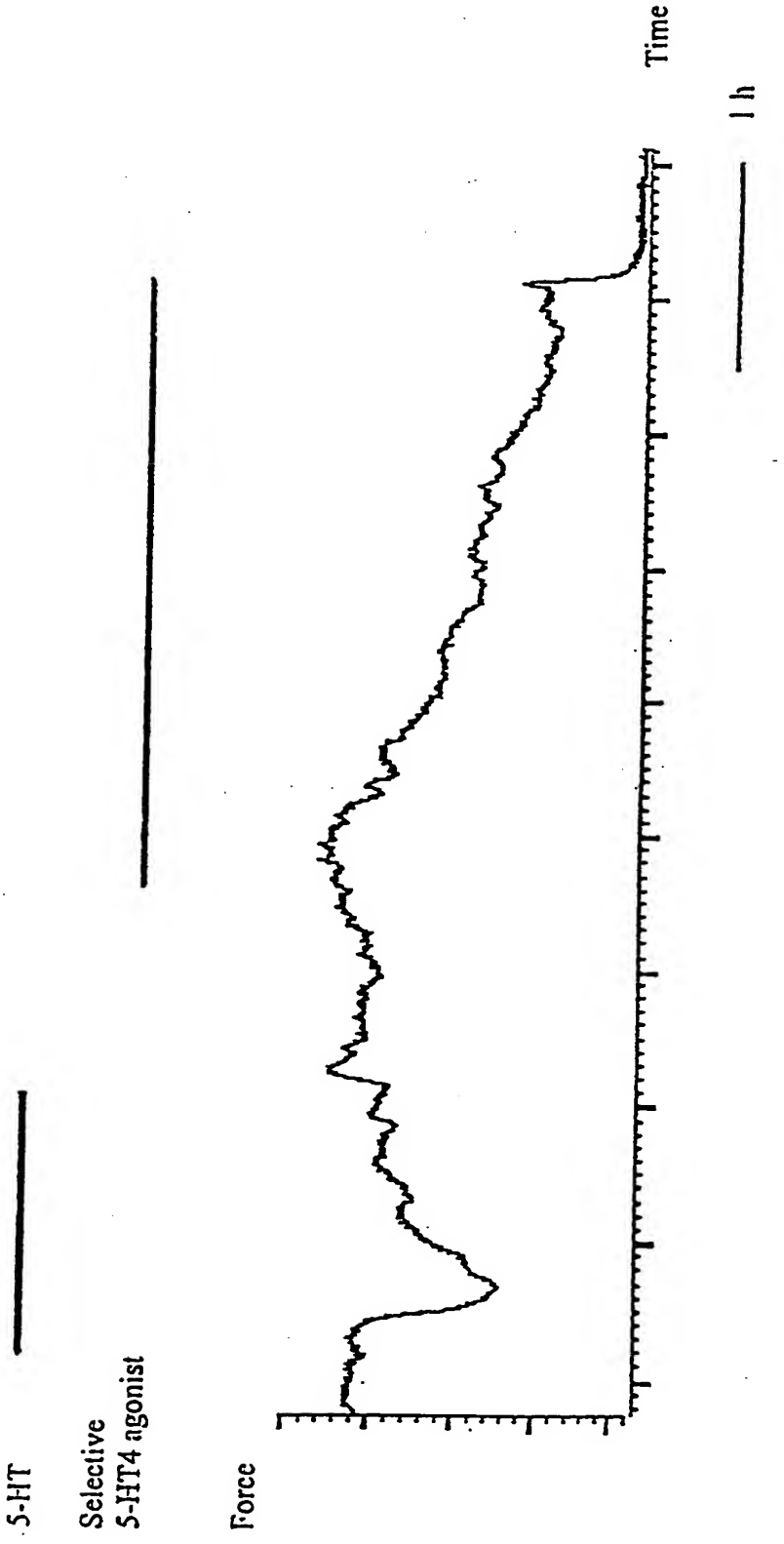


Fig 1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(22) International Filing Date: 15 June 2000 (15.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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9902252-7	15 June 1999 (15.06.1999)	SE
60/139,633	17 June 1999 (17.06.1999)	US
60/139,632	17 June 1999 (17.06.1999)	US
PCT/SE00/00819	28 April 2000 (28.04.2000)	SE

(71) Applicant *(for all designated States except US)*: **RESPIRATORIUS AB** [SE/SE]; Sölvegatan 41, S-223 70 Lund (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SKOGVALL, Staffan** [SE/SE]; Flygelvägen 33, S-224 72 Lund (SE).

(74) Agent: **AWAPATENT AB**; Box 5117, S-200 71 Malmö (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report:
12 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/76500 A3

(54) Title: COMPOUND FOR USE AS A MEDICAMENT FOR TREATMENT OF DISORDERS INVOLVING BRONCHOCONTRACTION

(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronochial asthma attack"; & 63015, SU,A1,1701320, 19911230 --	5
A	US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95) --	5
A	WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97) --	5

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2001	03 -04- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Lille Médical, Volume 16, No 5, 1971, F. Guerrin et al, "Effets du métoclopramide sur le bronchospasme expérimental du cobaye et sur le test à l'acétylcholine chez l'homme" page 731 - page 735	12
X	Arch.int.Pharmacodyn, Volume 165, No 2, 1967, J. Simke et al, "Bradykinin induced bronchoconstriction in guinea pigs and its modification by various agents" page 291 - page 301	12
X	British Journal of Anaesthesia, Volume 78, 1997, N. Otomo et al, "In vivo assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope" page 579 - page 582	12
X	Clinical and Experimental Pharmacology and Physiology, Volume 19, 1992, M.P. Rechtman, "Sensory nerves in the airways as a target for drug development" page 31 - page 39	12
X	Br.J.Pharmacol., Volume 101, 1990, M.P. Rechtman et al, "Effects of morphine, H-Tyr-D-Arg-Phe-Lys-NH2(DALDA) and B-HT920 on non-cholinergic nerve-mediated bronchoconstriction in pithed guinea-pigs" page 269 - page 272	12
X	ANESTH ANALG, Volume 72, 1991, Benoît Gentil et al, "Droperidol Prevents Serotonin-Induced Bronchospasm in the Guinea Pig" page 612 - page 615	12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Japan.J.Pharmacol., Volume 51, 1989, Shahin Sanjar et al, "The Effect of Prophylactic Anti-Asthma Drugs on PAF-Induced Airway Hyperreactivity" page 151 - page 160	12
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X	J.Pharmacobio-Dyn., Volume 12, 1989, Yoshio Tsuchiya et al, "Inhibition of the Vagal Reflex-Induced Tracheal Constriction by Psychotropic Drugs" page 437 - page 440	12
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X	EUROPEAN JOURNAL OF PHARMACOLOGY, Volume 6, 1969, Enrique Hong et al, "Similarities between the Pharmacological Actions of Quipazine and Serotonin" page 274 - page 280	12
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X	WO 8904660 A1 (BEECHAM GROUP PLC), 1 June 1989 (01.06.89)	12
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X	Proceedings of the Society for Experimental Biology and Medicine, Volume 184, 1987, L.B. Lipham et al, "Quipazine-Metoclopramide Inhibition of CB-154-Induced Prolactin Suppression in Rats: Neurotransmitter-Metabolite Correlations (42475)" page 250 - page 255	17
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X	Indian J Med Res, Volume 78, October 1983, T.J. Hemnani & P.G. Dashputra, "Potentiation of the psychotropic effect of chlorpromazine by metoclopramide" page 593 - page 595	17
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X	Anti-Cancer Drugs, Volume 7, 1996, Vittorio Gebbia et al, "Treatment of cisplatin-related nausea and vomiting with a combination of ondansetron and metoclopramide: a pilot study" page 734 - page 737	17
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Br.J Clin Pharmacol, Volume 41, 1996, D.T.T. Chua et al, "The antiemetic efficacy of tropisetron plus dexamethasone as compared with conventional metoclopramide-dexamethasone combination in Orientals receiving cisplatin chemotherapy: a randomized crossover trial" page 403 - page 408 --	17
X	Journal of Clinical Anesthesia, Volume 10, 1998, Richard A. Steinbrook et al, "Prophylactic Antiemetics for Laparoscopic Cholecystectomy: A Comparison of Perphenazine, Droperidol Plus Ondansetron, and Droperidol Plus Metoclopramide" page 494 - page 498 -- --------	17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01267

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7 and 16
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☒ Claims Nos.: 1-6,8-15 and 17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet*

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet**

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

*The claims contain a plurality of different compounds and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT to such an extent that a meaningful search of the whole scope of the claims is impossible.

Expressions such as "compound ... having agonist activity to a 5-HT4 receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Further, expressions such as "disorders involving bronchocontraction" and "derivatives" are not clear and concise.

Due to these deficiencies, a search has been carried out for those parts of the claims which appear to be supported and disclosed, namely claim 5 (invention 1), the part of claim 12 which refers to claim 11 (invention 2) and the combination of the compounds according to claims 5 and 12 (invention 3).

The search has been aimed at documents having explicit information of use for treatment of bronchocontraction.

The applicants attention is drawn to the fact that claims relating to those parts of the inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01267

**As is stated in Annex B to Administrative Instructions under the PCT, in force July 1, 1998, (PCT GAZETTE 1998, June 25, pp 45-50) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features"- i.e. features that define a contribution which each of the inventions makes over the prior art (cf. PCT Rule 13.2). This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

Invention 1. Claims 1-7 relating to a compound having agonist activity to a 5-HT4 receptor.
Invention 2. Claims 8-12 relating to a compound having antagonist activity to a 5-HT3 receptor.
Invention 3. Claims 13-17 relating to a composition comprising a combination of compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/01267

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/01267

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60/139,633	17 June 1999 (17.06.1999)	US
60/139,632	17 June 1999 (17.06.1999)	US
PCT/SE00/00819	28 April 2000 (28.04.2000)	SE

(71) Applicant *(for all designated States except US)*: **RESPIRATORIUS AB** [SE/SE]; Sölvegatan 41, S-223 70 Lund (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **SKOGVALL, Staffan** [SE/SE]; Flygelvägen 33, S-224 72 Lund (SE).

(74) Agent: **AWAPATENT AB**; Box 5117, S-200 71 Malmö (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 12 July 2001
Date of publication of the revised international search report: 16 August 2001

(15) Information about Correction:
see PCT Gazette No. 33/2001 of 16 August 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/76500 A3

(54) Title: COMPOUND FOR USE AS A MEDICAMENT FOR TREATMENT OF DISORDERS INVOLVING BRONCHOCONTRACTION

(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT_4 receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_3 receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

REVISED VERSION

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronochial asthma attack"; & 63015, SU,A1,1701320, 19911230 --	5
A	US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95) --	5
A	WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97) --	5

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2001	03 -04- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Lille Médical, Volume 16, No 5, 1971, F. Guerrin et al, "Effets du métoclopramide sur le bronchospasme expérimental du cobaye et sur le test à l'acétylcholine chez l'homme" page 731 - page 735	12
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X	British Journal of Anaesthesia, Volume 78, 1997, N. Otomo et al, "In vivo assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope" page 579 - page 582	12
X	Clinical and Experimental Pharmacology and Physiology, Volume 19, 1992, M.P. Rechtman, "Sensory nerves in the airways as a target for drug development" page 31 - page 39	12
X	Br.J.Pharmacol., Volume 101, 1990, M.P. Rechtman et al, "Effects of morphine, H-Tyr-D-Arg-Phe-Lys-NH2(DALDA) and B-HT920 on non-cholinergic nerve-mediated bronchoconstriction in pithed guinea-pigs" page 269 - page 272	12
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Japan.J.Pharmacol., Volume 51, 1989, Shahin Sanjar et al, "The Effect of Prophylactic Anti-Asthma Drugs on PAF-Induced Airway Hyperreactivity" page 151 - page 160	12
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01267

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Br.J Clin Pharmacol, Volume 41, 1996, D.T.T. Chua et al, "The antiemetic efficacy of tropisetron plus dexamethasone as compared with conventional metoclopramide-dexamethasone combination in Orientals receiving cisplatin chemotherapy: a randomized crossover trial" page 403 - page 408 --	17
X	Journal of Clinical Anesthesia, Volume 10, 1998, Richard A. Steinbrook et al, "Prophylactic Antiemetics for Laparoscopic Cholecystectomy: A Comparison of Perphenazine, Droperidol Plus Ondansetron, and Droperidol Plus Metoclopramide" page 494 - page 498 -- --------	17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01267

Box I **Observations where certain claims were found unsearchable (C ntinuation f item 1 f first sheet)**

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because they relate to subject matter not required to be searched by this Authority, namely:

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2. ☒ Claims Nos.: 1-6,8-15 and 17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet*

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See extra sheet**

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4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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Invention 2. Claims 8-12 relating to a compound having antagonist activity to a 5-HT3 receptor.

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